PRIVACY ACT MATERIAL REMOVED

SECTION I

Form Approved
Budget Bureau No. 68-R0249

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

GRANT APPLICATION

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TYPE	PROGRAM	NUMBER	718879
REVIEW GROUP		FORMERLY	
COUNCIL (Month, Year)		DATE RECEIVED	

TO BE COMPLETED BY PRINCIPAL INVESTIGATOR (Items 1 through 7 and 15A)

1. TITLE OF PROPOSAL (Do not exceed 53 typewriter spaces)

ORAU-ORNL STUDY OF CARBON-11 IN NUCLEAR MEDICINE (SUPPLEMENT) (deleted version)

2. PRINCIPAL INVESTIGATOR

2A. NAME (Last, First, Initial)

Hayes, Raymond L.

2B. TITLE OF POSITION

Senior Scientist

2C. MAILING ADDRESS (Street, City, State, Zip Code)

Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

2D. DEGREE: Ph.D.

2E. SOCIAL SECURITY NO.:

2F. TELEPHONE DATA: Area Code 615 | TELEPHONE NUMBER AND EXTENSION 483-8411 (243)

2G. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT (See Instructions)

Radiopharmaceutical

2H. MAJOR SUBDIVISION (See Instructions)

Medical Division

3. DATES OF ENTIRE PROPOSED PROJECT PERIOD (This application)

FROM	THROUGH
07-01-75	03-31-77

4. TOTAL DIRECT COSTS REQUESTED FOR PERIOD IN ITEM 3: $291,400

5. DIRECT COSTS REQUESTED FOR FIRST 12 MONTH PERIOD: $231,980

6. PERFORMANCE SITE(S) (See Instructions)

Medical Division
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

Congressional District 3

7. Research Involving Human Subjects (See Instructions)

A. ☐ NO B. ☒ YES Approved: 1/25/75 (Date)
C. ☐ YES – Pending Review

8. Inventions (Renewal Applicants Only - See Instructions)

A. ☐ NO B. ☐ YES – Not previously reported
C. ☐ YES – Previously reported Not Applicable

TO BE COMPLETED BY RESPONSIBLE ADMINISTRATIVE AUTHORITY (Items 8 through 13 and 15B)

9. APPLICANT ORGANIZATION(S) (See Instructions)

Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830

and

East Tennessee Cancer Research Center
IBM Building, 9040 Exec. Park Drive
Knoxville, Tennessee 37619

10. NAME, TITLE, AND TELEPHONE NUMBER OF OFFICIAL(S) SIGNING FOR APPLICANT ORGANIZATION(S)

Philip L. Johnson
Executive Director
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830
Telephone Number (615) 483-8411, ext. 301

11. TYPE OF ORGANIZATION (Check applicable item)

☐ FEDERAL ☐ STATE ☐ LOCAL ☒ OTHER (Specify)
Private: nonprofit

12. NAME, TITLE, ADDRESS, AND TELEPHONE NUMBER OF OFFICIAL IN BUSINESS OFFICE WHO SHOULD ALSO BE NOTIFIED IF AN AWARD IS MADE

Mr. J. W. Rose, Jr.
Assistant Treasurer
Oak Ridge Associated Universities
P. O. Box 117
Oak Ridge, Tennessee 37830
Telephone Number (AC 615) 483-8411;294

13. IDENTIFY ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT PURPOSES (See Instructions)

20. Other (Medical Division)

14. ENTITY NUMBER (Formerly PHS Account Number)

835981

15. CERTIFICATION AND ACCEPTANCE. We, the undersigned, certify that the statements herein are true and complete to the best of our knowledge and accept, as to any grant awarded, the obligation to comply with Public Health Service terms and conditions in effect at the time of the award.

SIGNATURES (Signatures required on original copy only. Use ink, "Per" signatures not acceptable)	A. SIGNATURE OF PERSON NAMED IN ITEM 2A	DATE
	B. SIGNATURE(S) OF PERSON(S) NAMED IN ITEM 10	DATE

NIH 398 (FORMERLY PHS 398)
Rev. 1/73

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

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RESEARCH OBJECTIVES

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PROJECT NUMBER

NAME AND ADDRESS OF APPLICANT ORGANIZATION

Oak Ridge Associated Universities, P. O. Box 117, Oak Ridge, Tennessee 37830

NAME, SOCIAL SECURITY NUMBER, OFFICIAL TITLE, AND DEPARTMENT OF ALL PROFESSIONAL PERSONNEL ENGAGED ON PROJECT, BEGINNING WITH PRINCIPAL INVESTIGATOR

Raymond L. Hayes, Principal Investigator, Medical Division, Senior Scientist

Bruce W. Wieland, Medical Division, Scientist,

Rasey F. Feezell, Medical Division, Instrument Engineer,

TITLE OF PROJECT

ORAU-ORNL STUDY OF CARBON-11 IN NUCLEAR MEDICINE (Supplement)

USE THIS SPACE TO ABSTRACT YOUR PROPOSED RESEARCH. OUTLINE OBJECTIVES AND METHODS. UNDERSCORE THE KEY WORD (NOT TO EXCEED 10) IN YOUR ABSTRACT.

This is a grant application supplemental to 1 ROl CA 14669 (initiated 04/01/74) that involves a program of identification, synthesis, and clinical testing of various ^{11}C-labeled compounds ($T_{1/2}$ ^{11}C = 20.5m) as possible nuclear medical agents for the external imaging of malignancies and specific organs in humans. Progress to date in this project has been substantial and it is now estimated that two of these ^{11}C-labeled agents (^{11}C-labeled 1-aminocyclopentanecarboxylic acid, a diagnostic agent for cancer, and DL-tryptophan, a pancreas-imaging agent) will come to clinical trials within the next 3-6 months.

Although ^{11}C-labeled agents were predicted initially to be diagnostically effective using conventional rectilinear scanning and positron camera instrumentation, the recent introduction of positron emission transaxial tomography (PETT) now offers a new imaging technique that will fully utilize the positron decay mode of ^{11}C (^{11}). Experimental results from PETT prototypes and a clinical PETT instrument made operational in January 1975 indicate that a dramatic improvement in spatial resolution for imaging the in vivo distribution of positron-emitting radiopharmaceuticals may be obtained. This device utilizes coincidence detection of ^{11}C positron annihilation radiation coupled with computerized reconstruction. The acquisition of the PETT positron-imaging instrumentation that is proposed in this supplement will provide an important additional definitive means of assessing the diagnostic potential of the ^{11}C-labeled radiopharmaceuticals being developed in grant project 1 ROl CA 14669.

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SECTION II – PRIVILEGED COMMUNICATION PRIVACY ACT MATERIAL REMOVED

9

DETAILED BUDGET FOR FIRST 12-MONTH PERIOD | FROM 7-1-75 | THROUGH 3-31-76

DESCRIPTION (Itemize)		TIME OR EFFORT %/HRS.	AMOUNT REQUESTED (Omit cents)		
PERSONNEL			SALARY	FRINGE BENEFITS	TOTAL
NAME	TITLE OF POSITION				
Hayes, R. L.	PRINCIPAL INVESTIGATOR	5%			
Wieland, B.	Scientist	10			
Feezell, R.	Mechanical Engineer	100			
Barclay, T.	Electronics Engineer	15			
Gibbs, W.	Research Associate IV	10			
Hansard, M.	Systems Analyst	35			
Akin, T.	Programmer II	75			

CONSULTANT COSTS None

EQUIPMENT

Electronics	$87,200
Interdata Computer (32K)	35,100
Movable Head Disc	12,000
Ramtec Display	15,000
Mechanical Systems	43,000

192,300

SUPPLIES Miscellaneous Electronic Components 1,500

TRAVEL

DOMESTIC To consult with the Edward Mallinckrodt Institute of Radiology at St. Louis, Mo. 600

FOREIGN

PATIENT COSTS (See instructions)

ALTERATIONS AND RENOVATIONS

Instrument Partitions	$750
Power Line Filter	400

1,150

OTHER EXPENSES (Itemize)

TOTAL DIRECT COST (Enter on Page 1, Item 5) 231,980

INDIRECT COST (See Instructions)

DATE OF DHEW AGREEMENT:

____ % S&W*

37.06 % TDC* 7-1-73

*IF THIS IS A SPECIAL RATE (e.g. off-site), SO INDICATE.

☐ WAIVED

☐ UNDER NEGOTIATION WITH:

[redacted]

SECTION II – PRIVILEGED COMMUNICATION PRIVACY ACT MATERIAL REMOVED

DETAILED BUDGET FOR 9 FIRST 12-MONTH PERIOD

FROM: 7-1-75 THROUGH: 3-31-76

DESCRIPTION (Itemize) PERSONNEL NAME	TITLE OF POSITION	TIME OR EFFORT %/HRS.	AMOUNT REQUESTED (Omit cents) SALARY	FRINGE BENEFITS	TOTAL
Hayes, R. L.	PRINCIPAL INVESTIGATOR	5%			
Wieland, B.	Scientist	10			
Feezell, R.	Mechanical Engineer	100			
Barclay, T.	Electronics Engineer	15			
Gibbs, W.	Research Associate IV	10			
Hansard, M.	Systems Analyst	35			
Akin, T.	Programmer II	75			

CONSULTANT COSTS None

EQUIPMENT

Electronics	$87,200
Interdata Computer (32K)	35,100
Movable Head Disc	12,000
Ramtec Display	15,000
Mechanical Systems	43,000

192,300

SUPPLIES Miscellaneous Electronic Componenrs 1,500

TRAVEL

DOMESTIC To consult with the Edward Mallinckrodt Institute of Radiology at St. Louis, Mo. 600

FOREIGN

PATIENT COSTS (See instructions)

ALTERATIONS AND RENOVATIONS

Instrument Partitions	$750
Power Line Filter	400

1,150

OTHER EXPENSES (Itemize)

TOTAL DIRECT COST (Enter on Page 1, Item 5) 231,000

INDIRECT COST (See Instructions)

_____ % S&W*

37.06 % TDC* 7-1-73

*IF THIS IS A SPECIAL RATE (e.g. off-site), SO INDICATE.

DATE OF DHEW AGREEMENT:

☐ WAIVED

☐ UNDER NEGOTIATION WITH: _____

NIH 398 (FORMERLY PHS 398) Rev. 1/73

[redacted]

BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED FROM PUBLIC HEALTH SERVICE
DIRECT COSTS ONLY (Omit Cents)

DESCRIPTION	1ST PERIOD (SAME AS DE FAILED BUDGET)	ADDITIONAL YEARS SUPPORT REQUESTED (This application only)					
		2ND YEAR	3RD YEAR	4TH YEAR	5TH YEAR	6TH YEAR	7TH YE
PERSONNEL COSTS	36,430*	57,520					
CONSULTANT COSTS (Include fees, travel, etc.)							
EQUIPMENT	192,300	-					
SUPPLIES	1,500	1,000					
TRAVEL DOMESTIC	600	600					
TRAVEL FOREIGN							
PATIENT COSTS	-	-					
ALTERATIONS AND RENOVATIONS	1,150	-					
OTHER EXPENSES	-	300					
TOTAL DIRECT COSTS	231,980	59,420					

TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Enter on Page 1, Item 4) ⟶ $ 291,400

REMARKS: *Justify all costs for the first year for which the need may not be obvious. For future years, justify equipment costs, as well as any significant increases in any other category. If a recurring annual increase in personnel costs is requested, give percentage. (Use continuation page if needed.)*

A. Equipment Justification:

Quotations for the electronic equipment, including the computer and display, were requested from the following companies: Searle Radiographics Inc., Des Plaines, Ill; ORTEC Inc., Oak Ridge, Tenn.; and Tennelec Inc., Oak Ridge, Tenn. Searle Radiographics Inc. was not able to submit a proposal in the short timespan available. The following preliminary quotations were received from the other two companies:

ORTEC Inc.

Electronics	$ 94,000
DEC Computer with 16K Floating Point CPU	38,000
Floppy Disc	7,000
Ramtec Display	15,000
Total	$154,000

Tennelec Inc.

Electronics	$ 87,200
Interdata Computer with 32K Fixed Point CPU	35,100
Movable Head Disc	12,000
Ramtec Display	15,000
Total	$149,300

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The design architecture proposed by these two firms is significantly different, each having its own advantages and disadvantages. A final technical definition of the electronics requirements is not possible at this time, and the figures presented do not represent identical approaches governed by a tight set of specifications. Final selection will be made after project funding is available, through a process of technical discussions and evaluations with these and other companies.

Combining the mechanical costs (see Methods of Procedure) with the lower of the two electronic quotations produces a total of:

Electronics, Computer, and Display	$149,300
Mechanical System	43,000
Total	$192,300

An investigation was made to determine the feasibility of building the complete instrument at ORAU in order to more exactly duplicate the work done at Washington University School of Medicine at St. Louis and, therefore, save money. However, the necessary digital electronics engineering manpower is not available within our organization and does not appear to be available from other sources on a short-term employment basis.

The specific equipment is needed for:

Electronics	$87,200	To detect the positron activity, collect the data and place it into the computer in the proper order.
Computer	35,100	To perform the reconstruction, position the mechanical portion of the instrument, and provide output of the data.
Disc Storage	12,000	Since the reconstruction algorithm uses all the core memory, some fixed storage will be required. The disc will also be used to store various control programs.
Ramtec Display	15,000	This oscilloscope device with 64 shades of gray intensity control will be used for output of the final reconstructed image.
Mechanical System	43,000	This equipment will provide the detector mounting and positioning controls along with the rotation motor and controls.
Total	$192,300	

B. Alterations:

An existing large room will need partitioning to isolate patients from the electronic equipment. Estimated cost, $750.00. Since the computer and other electronic equipment are sensitive to powerline noise, $400.00 will also be [redacted] a powerline filter.

Privileged Communication

C. Salary increases for the second year are computed at 10%. In addition, 10% of an electronics technician has been added during the second year for maintenance of the equipment. For changes in personnel time devoted to project during the second year, see Figure 14.

D. No changes have been made or are intended in the allocation of funds within categories for the previously approved corresponding periods of the project.

E. * It is recognized that the normal earliest starting date for funding an application is September 1 of the same year when an application is made as of February 1. However, in the instructions form for grant application (Form 398,p.1) it is stated that special consideration may be given to changes in this schedule. We have accordingly based our proposal on a starting date of July 1, 1975, since we believe that it is imperative (in view of the progress made to date on the grant as originally funded and the potential that now appears to exist) that we should proceed as rapidly as possible in order to realize the maximum benefit that this project affords. We, therefore, request that this supplemental proposal be given special consideration for July funding. Should this application be approved but not funded until September 1 (or later), it is obvious that certain decreases will be required in the approved funding (particularly for personnel expenses), since the first performance period will be six months rather than nine months.

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SECTION II – PRIVILEGED COMMUNI[illegible] ON

BIOGRAPH[illegible]AL SKETCH

(Give the following information for all professional per[illegible]el listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow[illegible] same general format for each person.)

NAME	TITLE	BIRTHDATE *(Mo., Day, Yr.)*
Raymond L. Hayes	Senior Scientist	
PLACE OF BIRTH *(City, State, Country)*	**PRESENT NATIONALITY** *(If non-U.S. citizen, indicate kind of visa and expiration date)*	**SEX**
	USA	☒ Male ☐ Female

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
University of North Carolina Chapel, N. C.	B.S.	1944	Chemistry
University of North Carolina Chapel, N.C.	Ph.D.	1952	Organic Chemistry

HONORS

Sigma Xi; AEC (NSF) Predoctoral Fellowship 1948-1950

MAJOR RESEARCH INTEREST	ROLE IN PROPOSED PROJECT
Radiopharmaceutical development	Principal Investigator

RESEARCH SUPPORT *(See instructions)*

NIH Grant I ROl CA 11858 RAD, "Concentration of Radionuclides by Malignant Neoplasms," includes 35% of salary and benefits. Approved budget 05/01/74 through 04/30/75: $68,189. 05/01/73 - 04/30/76: $205,938.

NIH Grant 1 ROl CA 14669 "ORAU-ORNL Study of Carbon-11 in Nuclear Medicine" includes 15% of salary and benefits. Approved budget 04/01/74 - 03/31/75: $85,000; 04/01/74 - 03/31/77: $329,275.

Fifty percent of salary and other research support is through ERDA Contract No. AT-40-1-Gen 33.

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

Senior Scientist, Medical Division, Oak Ridge Associated Universities, Oak Ridge, Tenn. 1950 - present.
Senior Chemist, U. S. Rubber Co., Charlotte, North Carolina, 1944

Publications:

Washburn, L.C., Carlton, J.E., Hayes, R.L., and Yuhas, J.M. Distribution of WR-2721 in normal and malignant tissues of mice and rats bearing solid tumors: Dependence on tumor type, drug dose and species. Radiat. Res. 59:475-483, 1974.

Brown, D.H., Carlton, E., Byrd, B., Harrell, B., and Hayes, R.L. A rate-zonal centrifugation procedure for screening particle populations by sequential product recovery utilizing edge-unloading zonal rotors. Arch. Biochem. Biophys. 155:9-18, 1973.

Brown, D.H., Swartzendruber, D.C., Carlton, J.E., Byrd, B.L., and Hayes, R.L. The isolation and characterization of gallium-binding granules from soft tissue tumors. Cancer Res. 33:2063-2067, 1973.

Hayes, R.L. and Carlton, J.E. A study of the macromolecular binding of ^{67}Ga in normal and malignant animal tissues. Cancer Res. 33:3265-3272, 1973.

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Hayes, R. L. and Edwards, C. L. New applications of tumour-localizing radiopharmaceuticals. In: Medical Radioisotope Scintigraphy, 1972. Proceedings of a Symposium, Monte Carlo, IAEA, 1973, pp. 531-552.

Hayes, R. L., Rafter, J. J., Washburn, L. C., and Byrd, B. L. Affinity of ^{253}einsteinium for tumour tissue. Nat. New Biol. 246: 23-25, 1973.

Edwards, C. L., and Hayes, R. L. Localization of tumors with radioisotopes. In: Proceedings of Clinical Uses of Radionuclides: Critical comparison with other techniques, Oak Ridge, Tennessee, 1971, USAEC Report CONF 711001.

Brown, D. H., Swartzendruber, D. C., Carlton, J. E., Byrd, B. L., and Hayes, R. L. Mechanism of gallium-binding in tumors: Isolation and characterization of gallium binding-granules (GBG) in soft tissue tumors. Proc. Amer. Assoc. Cancer Res. 13: 37, 1972 (abstr.).

Nelson, B., Hayes, R. L., Edwards, C. L., Kniseley, R. M., and Andrews, G. A. Distribution of gallium in human tissues after intravenous administration. J. Nucl. Med. 13: 920100, 1972.

Swartzendruber, D. C., Nelson, B., and Hayes, R. L. Gallium-67 localization in lysosomal-like granules of leukemic and nonleukemic murine tissues. J. Nat. Cancer Inst. 46: 941-952, 1971.

Hayes, R. L., Nelson, B., Swartzendruber, D. C., Brown, D. H., Carlton, J. E., and Byrd, B. L. Studies of the intracellular deposition of ^{67}Ga. J. Nucl. Med. 12: 364, 1971. (abstr.)

Edwards, C. L., and Hayes, R. L. Scanning malignant neoplasms with gallium-67. JAMA 212: 1182-1190, 1970.

Bernard, S. R., and Hayes, R. L. Dose to various segments of the gastrointestinal tract In: Medical Radionuclides: Radiation Dose and Effects, proceedings of a symposium, Oak Ridge Associated Universities, December 1969, USAEC Symposium Series No. 20, CONF 691212, 1970, pp 295-313.

Hayes, R. L., Nelson, B., Swartzendruber, D. C., Carlton, J. E., and Byrd, B. L. Gallium-67 localization in rat and mouse tumors. Science 167: 289-290, 1970.

Kniseley, R. M., Andrews, G. A., Edwards, C. L., and Hayes, R. L. Bone marrow and skeletal scanning. In Radiologic Clinics of North America (E. R. King, special ed.) Vol. VII, August 1969, pp 265-280.

Hartman, R. E., and Hayes, R. L. The binding of gallium by blood serum. J. Pharmacol. Exp. Therap. 168: 193-198, 1969.

Radioisotopes in Medicine: In Vitro Studies. Proceedings of a symposium held at the Oak Ridge Associated Universities, November 13-16, 1967. R. L. Hayes, F. A. Goswitz, and B. E. P. Murphy, eds. USAEC Symposium Series No. 13, CONF-67111, June 1968, 753 pp.

Hayes, R. L., Byrd, B. L., and Carlton, J. E. ^{113m}In as a possible bone scanning agent. J. Nucl. Med. 9: 323, 1968. (abstr.)

Hayes, R. L., Carlton, J. E., Byrd, B. L., and Rafter, J. J. Factors influencing the distribution of labeled hydrous ferric oxide colloid. J. Nucl. Med. 8: 302, 1967 (abstr.).

Hayes, R. L., Carlton, J. E., and Raft[illegible], J. J. Scanning with hydrous ferric oxide colloid labeled with gallium-68. J. Nucl. Med. 7: 335-336, 1966. (abstr.)

Hayes, R. L. Radioisotopes of gallium. In: Radioactive Pharmaceuticals, edited by G. A. Andrews, R. M. Kniseley, and H. N. Wagner, Jr., AEC Symposium Series No. 6, CONF-651111, April 1966, pp. 603-618.

Hayes, R. L., Carlton, J. E., and Byrd, B. L. Bone scanning with gallium-68. A carrier effect. J. Nucl. Med. 6: 605-610, 1965.

Hayes, R. L., Oddie, T. H., and Brucer, M. Dose comparison of two total-body irradiation facilities. Int. J. Appl. Radiat. Isotop. 15:313-318, 1964.

Hayes, R. L., Carlton, J. E., and Nelson, B. Lanthanum-140 as a measure of the completeness of stool collections. Demonstration of delayed excretion of iron-59. J. Nucl. Med. 5: 200-208, 1964.

Hayes, R. L., Carlton, J. E., and Butler, W. R., Jr. Radiation dose to the human intestinal tract from internal emitters. Health Phys. 9: 915-920, 1963.

Simon, N., Brucer, M., and Hayes, R. Radiation and leukemia in carcinoma of the cervix. Radiology 74: 905-911, 1960.

Hayes, R.L., Nold, M.M., Comar, C.L., and Kakehi, H. Internal radiation dose measurements in live experimental animals. Part 1. Health Phys. 4:79-85, 1960.

Nold, M.M., Hayes, R.L., and Comar, C.L. Internal radiation dose measurements in live experimental animals. Part 2. Health Phys. 4:86-100, 1960.

Hayes, R. L., and Brucer, M. Compartmentalized phantoms for the standard man, adolescent, and child. Int. J. Appl. Radiat. Isotop. 9:113-118, 1960.

Hayes, R. L., and Butler, W. R., Jr. Growth and decay of radionuclides. A demonstration. J. Chem. Educ. 37: 590-592, 1960.

Hayes, R. L. Chemical measurement of integral dose. In: Roentgens, Rads, and Riddles Milton Friedman, Marshall Brucer, and Elizabeth B. Anderson, eds. United States Atomic Energy Commission, 1959, pp. 61-68.

Harris, N. O., and Hayes, R. L. A tracer study of the effect of acute and chronic exposure to sodium fluoride on the thyroid iodine metabolism of rats. J. Dent. Res. 34: 470-477, 1955.

Bruner, H. D., Hayes, R. L., and Perkinson, J. D., Jr. A study of gallium-72. X. Preliminary data on gallium-67. Radiology 61: 602-612, 1953.

Bruner, H. D., Perkinson, J. D., Jr., and Hayes, R. L. Effect of quantity of carrier gallium on distribution of metal in rats. Fed. Proc. 11: 328: 1952. (abstr.)

Roe, A., Hayes, R. L., and Bruner, H. D. The purity of diiodofluorescein-I_2. J. Amer. Chem. Soc. 73: 4483, 1951.

Roe, A., Hayes, R. L., and Bruner, H. D. Study of the conditions involved in the preparation of 3, 4-diiodo-4-oxo-1-pyridine-acetic acid (diodrast) containing iodine-131. J. Elish Mitchell Sci. Soc. 66 (2), December 1950.

SECTION II – PRIVILEGED COMMUNICATION

PRIVACY ACT MATERIAL REMOVED

BIOGRAPHICAL SKETCH

(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
WIELAND, Bruce W.	Scientist	
PLACE OF BIRTH (City, State, Country)	**PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)**	**SEX**
	USA	☒ Male ☐ Female

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
Iowa State University, Ames, Iowa	B.S.	1960	Mechanical Engineering
Oak Ridge School of Reactor Technology Oak Ridge, Tenn.	Postgrad. certificate	1965	Nuclear Engineering
Ohio State University, Columbus, Ohio	Ph.D.	1973	Biomedical Nuclear Engineering

HONORS NIH Special Research Fellow, 1968-1973
Pi Tau Sigma (National Honorary Mechanical Engineering Fraternity), 1957 to present

MAJOR RESEARCH INTEREST	ROLE IN PROPOSED PROJECT
Biomedical applications of short-lived cyclotron-produced isotopes.	Biomedical Nuclear Engineer

RESEARCH SUPPORT *(See instructions)*

NIH Grant 1 RO1 CA 14669 "ORAU-ORNL Study of Carbon-11 in Nuclear Medicine" includes 80% of salary and benefits. Approved budget 04/01/74 - 03/31/75: $85,000; 04/01/74 - 03/31/77: $329,275.

Twenty percent of salary and other research support is through ERDA Contract No. AT-40-1-Gen 33.

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

Scientist, Medical Division, Oak Ridge Associated Universities, Oak Ridge, Tenn., 1974 to present.
Consultant, Medical Division, Oak Ridge Associated Universities, Oak Ridge, Tenn., 1973.
Research Associate and NIH Special Fellow in Radiology, The Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Mo., 1971-1973.
Research Engineer, Battelle Memorial Institute, Columbus, Ohio, 1967-1968.
Program Engineer and Nuclear Analyst, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1960-1966.

Publications

1. Development and Evaluation of Facilities for the Efficient Production of Compounds Labeled with Carbon-11 and Oxygen-15 at the Washington University Medical Cyclotron, B. W. Wieland, dissertation accepted by The Ohio State University, December 1973.
Phelps, M.E. and Wieland, B.W. Production of short-lived isotopes by charged particle accelerators. In Physics in Medicine and Biology, Vol. 18, No. 2, 284-286, March 1973.
Keilholtz, G.W., Moore, R.E., Osborne, M.F., Wieland, B.W., and Zulliger, A.F. Techniques for irradiating high temperature materials in a steep flux gradient, In Proceedings of the May 1966 International Symposium on Capsule Irradiation Experiments, Pleasanton, Calif.
Wieland, B. W. Analysis of the High Flux Isotope Reactor fuel element shipping cask (shielding analysis, Provisions for criticality control, Provisions for ruptured fuel elements), ORNL-TM-959, January 1965.

[redacted]

Biographical Sketch: B. W. Wieland

Publications (continued)

5. Llewellyn, G.A. and Wieland, B.W. Temperature distributions in fuel samples irradiated in Engineering Test Reactor lattice position J-12. ORNL-CF-64-5-60, May 1964.

6. Wieland, B.W. Review of stress calculations for Tower Shielding Reactor II (Shield and supports, Vertical scanning components). ORNL-CF-63-5-30, May 1963.

SECTION II – PRIVILEGED COMMUNICATION

PRIVACY ACT MATERIAL REMOVED

BIOGRAPHICAL SKETCH

(Give the following information for all professional personnel listed on page 3, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)
RASEY R. FEEZELL	Engineer	
PLACE OF BIRTH (City, State, Country)	**PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)**	**SEX**
	USA	☒ Male ☐ Female

EDUCATION *(Begin with baccalaureate training and include postdoctoral)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
University of Tennessee, Knoxville, Tenn.	B.S.	1965	Electrical Engineering
University of Tennessee, Knoxville, Tenn.	M.S.	1967	Electrical Engineering (Control Systems)

HONORS

Member ETA Kappa Nu (Electrical Engineering Honor Society)

MAJOR RESEARCH INTEREST	ROLE IN PROPOSED PROJECT
Instrumentation development.	Project engineer responsible for overall instrument development.

RESEARCH SUPPORT *(See instructions)*

None.

RESEARCH AND/OR PROFESSIONAL EXPERIENCE *(Starting with present position, list training and experience relevant to area of project. List all or most representative publications. Do not exceed 3 pages for each individual.)*

Professional Experience

1959 - Sept. 1974, Development specialist, Development Division, Y-12 Plant, Union Carbide Nuclear Company, Oak Ridge, Tennessee: worked with state of the art precision machining and inspection machines through the use of computers and advanced control systems techniques.

Publications

1. Feezell, R.R., and Marcum, R.C. Elimination of phase distortion in filters using digital techniques: Union Carbide Corp., Oak Ridge, Y-12 Plant, Document Y-DA-3514

9.

Automatic centering and inspection machine. Union Carbide Corp., -12 Plant, Document Y-1594, October 1967.

o the above, approximately 25 secret reports were written from

September-196

2. Feezell, R.R. Oak Ridge, Y-

3. In addition t 1959 to 1974.

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RESEARCH PLAN

A. Introduction:

1. Objective:

It is proposed that recently developed transaxial tomographic instrumentation be employed in the clinical testing of the various ^{11}C-labeled compounds that are now being developed in the parent project (1 ROl CA 14669) so that the positron character of ^{11}C can be utilized to its fullest in the clinical evaluation of these ^{11}C-labeled agents as radiopharmaceuticals for the detection of cancer and the imaging of specific organs in man.

2. Background:

Summary. With grant support from National Institutes of Health, Oak Ridge Associated Universities (ORAU) and Oak Ridge National Laboratory (ORNL) have recently initiated a study of the potential usefulness of a series of ^{11}C-labeled agents in nuclear medical imaging procedures. Progress has been unusually rapid, and we anticipate that two such radiopharmaceuticals will shortly be brought to clinical trials (one a tumor-localizing agent and the other an agent for pancreas visualization). In view of certain recent developments in positron instrumentation that hold high promise for greatly increased resolution of positron emitters such as ^{11}C, we are submitting this proposal for supplemental grant support so that we may be in a position to make use of this "state of the art" advancement in our clinical trials of these two agents and of others that will be forthcoming during the course of the ongoing study.

Basis for existing grant (1 ROl CA 14669). Although considerable progress has been made in the field of radiopharmaceutical development within recent years, the radionuclides presently in use for external imaging (^{99m}Tc, ^{67}Ga, ^{111}In, $^{131,125}I$-labeled compounds, etc.) all constitute to some extent foreign labels that have been in many cases chemically manipulated to produce the desired localizing properties. This approach to the development of radiopharmaceuticals has indeed been very rewarding, but the extent to which this type of manipulation can be employed has obvious limitations.

It has long been recognized that direct incorporation of a radioactive label as part of the basic structure of potential organic and biologically active radiopharmaceutical agents would be highly desirable, since such incorporation would produce no alterations in their in vivo behaviors as often happens when foreign labels are used. Of more importance, use of such labeled compounds, by the very nature of organic chemistry, would open up an indeed almost unlimited field of external imaging agents for investigation and potential use in diagnostic nuclear medicine. This approach requires the use of the short half-life radionuclides of carbon, nitrogen, and oxygen (^{11}C, $T_{1/2}$ = 20.5m; ^{13}N, $T_{1/2}$ = 10m; and ^{15}O, $T_{1/2}$ = 2m). Although the use of these radionuclides is complicated by their short half-lives, they do offer another great potential advantage in that they each decay by positron emission and hence could be used with coincidence type detection systems, a type of instrumentation long recognized to have high theoretical promise for imaging. Of these three radionuclides, ^{11}C is perhaps of most interest because of its higher abundance in organic compounds and, more important, its longer half-life

Research Plan: Background

ORAU and ORNL submitted in September 1972 a joint application for a Research Grant entitled "ORAU-ORNL Study of Carbon-11 in Nuclear Medicine." This proposal was approved and funded as of April 1, 1974 (1 RO1 CA 14669). Our approach involves use of incorporation data from test animals for the corresponding ^{14}C-labeled compounds as guidelines to the value of any potential ^{11}C-labeled compound. No procedures are to be developed for ^{11}C labeling until a useful incorporation pattern and time scale have been obtained. Ideas as to compounds of interest are being obtained from ^{14}C incorporation data in the literature or in our own studies.

Advantage is now being taken of the long-standing collaborative arrangements between ORAU and the Isotopes Development Center at ORNL in our present ongoing ^{11}C project. ORNL is supplying the ^{11}C production facilities and ORAU is devising the synthetic procedures and will carry out clinical trials. Initial labeling procedures will be carried out in shielded facilities at the ORNL 86-inch cyclotron complex. This complex is approximately 8 minutes in transit time from the ORAU facilities.

The 86-inch cyclotron has the unique capability of developing and accelerating such large internal proton beam currents (up to 2500 μA of 22 MeV protons) that most irradiations are limited only by energy dissipation. In addition the very large orbital separation in this cyclotron allows internal-beam target geometries that would require external beam bombardment at other cyclotrons.

The short half-life of ^{11}C obviously requires very rapid synthesis and purification of labeled compounds prior to administration, as well as suitable uptake and localization kinetics for the physiological system under investigation. The availability of multicurie quantities, i.e., >10 Ci, of ^{11}C will permit the use of either low-yield synthetic techniques or reaction schemes that require relatively long times for synthesis and purification, since in effect the ^{11}C will be expendable. This should enable us to synthesize and purify compounds that are more complex than is possible at other cyclotron installations.

Four possible compounds were identified as potential imaging agents for labeling with ^{11}C in the initial grant application (1-aminocyclopentanecarboxylic acid, DL-tryptophan, estradiol, and thymidine). Since then two other compounds have also been added to the list (ethidium bromide and hyaluronidase). These materials have all shown rapid uptake in tumor or pancreas either in reports in the literature or in our own animal experiments. In our work so far on this project, rapid synthesis and purification procedures have been developed for 1-aminocyclopentanecarboxylic acid (ACPC) and DL-tryptophan, and initial target design, preliminary to the production of $H^{11}CN$, is nearing completion (see comprehensive progress report). We anticipate that these two ^{11}C-labeled agents will go to clinical trial within the next 3-6 months.

Our present plans for clinical trials of ^{11}C-labeled ACPC and tryptophan involve using a standard Nuclear-Chicago Phogamma III scintillation camera equipped with a positron attachment and a conventional Ohio-Nuclear dual head whole-body scanner with coincidence capability. We propose with the supplemental support being requested in this application to add a state of the art positron transaxial tomographic imaging device to our instrumentation. With this instrument we anticipate being able to utilize the positron character of ^{11}C to its fullest in our clinical investigations. This proposal has been approved by the Scientific Review Committee of the East Tennessee Cancer Research Center.

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Research Plan: Backgr[illegible]nd

PRIVACY ACT MATERIAL REMOVED

Nuclear Medicine Imaging Devices. Instruments used in nuclear medicine for imaging the internal distribution of radionuclides can be broadly classified into scanners, cameras, and hybrid devices employing some features of both. The image-forming logic of these instruments is based either on collimated single-photon counting (SPC), or on annihilation coincidence detection (ACD) of the 511 KeV photons associated with positron decay. Imaging devices can be designed to detect radiation coming from the entire thickness of the subject in the field of view, or to operate in a tomographic mode.

In tomography, two different approaches are utilized to emphasize a selected plane at the expense of other planes in order to provide an image largely unaffected by activity contained in structures lying outside the plane of interest i.e,blurring of parallel longitudinal planes, and computerized reconstructive tomography.

The technique applied to scanners and cameras utilizing SPC and collimators is to blur out longitudinal planes parallel to the plane of interest. Spatial resolution and image contrast are severely limited by the depth-dependent sensitivity of the SPC collimator systems. Conventional positron cameras using ACD also apply this technique, but scintillation cameras are not particularly suitable for ACD because of their low efficiency (due to the thin crystal used) and their relatively long dead times.

The other technique is called computerized reconstructive tomography (usually transverse). Detectors looking edgewise at the plane of interest are rotated about the subject to provide information at several different angles. The resulting data is processed by a suitable mathematical algorithm to produce an image. This technique has been applied by Kuhl (1-4) to collimated SPC systems. Transaxial tomographic reconstructions using a SPC scintillation camera have also been used (5, 6). Brownell has developed a particularly successful positron camera system (7, 8) and has used it to produce transaxial tomographic images (9, 10) although it was not designed specifically for that purpose.

Positron Emission Transaxial Tomography (PETT). Ter-Pogossian and Phelps (11, 12) have investigated the use of ACD in transaxial reconstruction tomography by constructing a prototype device called the PETT (positron emission transaxial tomograph). This instrument is very similar in concept to the recently introduced EMI X-ray scanner (13) which employs a high contrast, narrow-beam scanning technique. The EMI device removes the superimposition of information with a mathematical algorithm to produce tomographic images of exceptional resolution and contrast unattainable by conventional radiographic methods. Many of the imaging improvements brought to diagnostic radiology by the EMI scanner can also be brought to nuclear medicine by the PETT system.

Ter-Pogossian and Phelps have just completed the construction of a large PETT system in Jan. 1975. Phantom studies and clinical evaluations have begun. This device has 48 NaI scintillation detectors placed in a hexagonal array (8 to a side) and arranged to view a 1 cm transaxial slice edgewise. Computer control accomplishes translation of the detectors along the sides of the hexagon and also rotates the hexagon. This results in the equivalent of a series of rectilinear scans at a number of discrete angles about the cross section of interest. ACD is achieved by connecting the detectors on opposing sides of the hexagon in cross-coincidence. This scheme provides a narrow-beam detection region with depth-independent sensitivity for annihilation photons emitted in the well-defined volume between any two detectors connected in coincidence. The absolute sensitivity can be calculated due

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to the fact that the sum of the attenuated path lengths for the two photons is always a constant regardless of the location of the positron annihilation. An algorithm is applied by the computer to transform the data into a final image. A more detailed description and explanation of the PETT system will be found in the "Methods of Procedure" section of this proposal.

Potential of the PETT System. Phantom and animal experiments with the previous PETT prototypes (11,12) demonstrated a potential for a clinical system that significantly complements the diagnostic protocols currently available in nuclear medicine. Spatial resolution may be a factor of two or more better than that available with current imaging devices. Contrast is predicted to be quantitative (object and image contrast equal) for objects equal to or greater than twice the spatial resolution. Cold spot contrast in the prototypes was particularly impressive compared to scintillation camera images. There was virtually no image degradation caused by activity distributions in immediately adjacent planes. Phantom and patient studies with the newly-contributed clinical PETT instrument began in January 1975.

In addition to ^{11}C there are a number of positron-emitting radionuclides with physical and chemical properties very favorable for applications to nuclear medicine imaging with the PETT system. Gallium-68 ($T_{1/2}$ = 68m) is available from a generator system (272 d, ^{68}Ge) and is a positron-emitting analog to ^{67}Ga, an important and well recognized isotope in nuclear medicine. Cyclotron produced ^{18}F, ^{13}N, and ^{15}O are currently used in physiological measurements. Iron-52, various rare earth radionuclides and copper-64 are two additional possibilities. Thus the dedication of the PETT system to positron emitters may not be as restrictive as are the limitations imposed by the scintillation camera's dependence on low photon energies, and the labeling limits caused by the chemical properties of ^{99m}Tc (11).

The availability of a PETT system for determining the in vivo distribution of positron-emitting radiopharmaceuticals with greatly increased accuracy would be an important and immediate asset to our ^{11}C studies. Complementary studies with our conventional scanning and camera devices would be used to augment the proposed PETT system.

3. Rationale:

As an adjunct to ongoing work on a grant entitled "ORAU-ORNL Study of Carbon-11 in Nuclear Medicine," we propose to fabricate a state of the art transaxial tomographic scanner for high resolution positron imaging of ^{11}C-labeled compounds that are now under development. We will draw on the experience that others have had with prototype models of this instrument. One of two alternative plans of construction and testing will be employed. When placed into clinical use this instrument should greatly enhance our ability to image the ^{11}C-labeled agents being developed in the parent grant.

4. Comprehensive Progress Report (1 RO1 CA 14669):

a. Period: 1 April 1974 - 15 January 1975

b. Summary:

Methods have been devised for the rapid synthesis and purification of ^{11}C-labeled 1-aminocyclopentanecarboxylic acid (2-step synthesis, 10 minutes) and DL-tryptophan (2-step synthesis, 17 minutes). The former is a potential tumor-localizing agent and the latter a potential pancreas-imaging agent. Both materials

can be quickly purified by an ion exchange technique. The effect of specific activity has been determined for both agents in animal studies. The tissue distribution of ACPC does not appear to be affected by the dose level while that of tryptophan does. Target design for the production of high levels of $^{11}CO_2/^{11}CO$ and $H^{11}CN$ for ^{11}C synthesis of the two amino acids is now in progress. It is anticipated that both compounds will go to clinical trials within 3-6 months.

c. Detailed Progress Report

Synthesis Studies. Considerable progress has been made in the synthesis and purification of two agents described in the original grant proposal, 1-aminocyclopentanecarboxylic acid (ACPC) and DL-tryptophan. ACPC labeled with ^{11}C is a promising tumor-scanning agent, quite possibly of general utility, while ^{11}C-labeled DL-tryptophan is potentially an excellent pancreas-scanning agent.

The major consideration in the development of methods of synthesis and purification has been the time involved. The short half-life of ^{11}C demands that short reaction times and rapid purification procedures be employed. These techniques have been developed using the analogous ^{14}C-labeled materials.

Experimental yields have been estimated by a procedure involving thin-layer chromatography (tlc). The ^{14}C reaction mixture is spotted on a tlc plate. After development with the proper solvent system, the radioactive spots are visualized by means of a spark chamber (Birchover Instrument Company). This allows a visual estimation of the amounts of each radioactive component, and thus the yield of the reaction may be estimated. Similar techniques may be employed to ascertain the purity of samples obtained from the trial of various purification methods.

ACPC is synthesized by a modified Strecker amino acid synthesis, a general method for the synthesis of many common amino acids. For ACPC this involves the treatment of cyclopentanone with ammonium carbonate, ammonium chloride, and potassium cyanide (labeled with ^{14}C in the development work) to form the hydantoin which is then hydrolyzed with barium hydroxide to the amino acid. This procedure has been used previously (14, 15) to prepare both unlabeled ACPC and the ^{14}C-labeled compound as well. However, reaction times of several hours were involved for each step, and the purification schemes employed were not at all feasible for a ^{11}C synthesis. It was found that by simply increasing the temperature and running the reaction in a stainless steel pressure vessel that the reaction time was enormously decreased. For example, using a reaction temperature of 210°C and a reaction time of 4 minutes for the first step and 6 minutes for the second step, an excellent yield of ACPC was achieved (roughly 70% based on visual examination of the spark chamber photograph of the tlc plate). A total reaction time of 10 minutes is quite in line with the requirements for ^{11}C synthesis.

The method of choice for purifying the reaction mixture involves (1) addition of sodium carbonate to precipitate the ionic barium as barium carbonate, (2) filtration to remove the barium carbonate, (3) boiling the basic solution while nitrogen is bubbled through to expel the ammonia, (4) acidification followed by boiling the acidic solution to expel any unreacted cyanide and carbon dioxide (from carbonates). All four steps can be rapidly and easily carried out in a hot cell using the semi-automated chemistry apparatus which is described later. The acidic solution is then subjected to column chromatography on a cation exchange resin. The protonated amino acid is bound strongly to the resin while the impurities, chiefly the intermediate hydantoin and unreacted cyclopentanone, are not.

Research Plan: Comprehensive Progress Report PRIVACY ACT MATERIAL REMOVED

Impurities may be removed by washing with 0.1 N hydrochloric acid and water. The pure amino acid is then eluted with 0.1 N sodium hydroxide. A very coarse cation exchange resin with a low percentage crosslinkage (AG50W-X4, 20-50 mesh, sodium form [Bio-Rad Laboratories]) was found to give excellent separation and also the rapid flow characteristics necessary for a fast separation.

The synthesis of tryptophan has been in most respects analogous. The synthetic method given in the original proposal, involving first synthesis of serine by a Strecker synthesis followed by an enzymatic condensation of serine with indole to yield tryptophan, was doubtful at best. An alternative pathway (16) was discovered involving a Strecker-type synthesis on 1-acetyl-3-indoleacetaldehyde semicarbazone. This is a derivative of the unstable aldehyde which apparently reacts similarly to the parent aldehyde under Strecker conditions to yield the hydantoin. (The semicarbazone is stockpiled and used as a starting material for the radioactive synthesis.) An estimated yield of DL-tryptophan ranging from 10-20% has been achieved using a total reaction time of 17 minutes - 7 minutes for the first step and 10 minutes for the second step. With our multicurie capacity for ^{11}C production, the low yield presents no problem as long as we can isolate the pure product in a rapid fashion. Purification techniques similar to those used for ACPC have been adapted to tryptophan. One difference is that it is helpful to incorporate an ethanol wash of the ion exchange resin to remove organic side products prior to elution with 0.1 N sodium hydroxide.

Since the Strecker amino acid synthesis is quite general, we feel that we have the potential for synthesizing many ^{11}C-labeled amino acids which are of interest in biochemistry and medicine. We are also very interested in the potential value of ^{11}C-labeled estradiol in breast tumor and pancreas scanning, although no work has yet been done on a rapid synthetic route leading to either this compound or the other proposed agents, thymidine, ethidium bromide, and hyaluronidase.

Animal Studies. Work which was cited in the original proposal demonstrated the potential value of ^{11}C-labeled 1-aminocyclopentanecarboxylic acid (ACPC) as a tumor-scanning agent. To briefly summarize that study, we examined the incorporation of ^{14}C-labeled ACPC into the various tissues of rats bearing the Morris 5123C hepatoma as a function of time. We found a maximum tumor incorporation at a postinjection time of 30 minutes, a very compatible time scale for ^{11}C studies. At this time the tumor-to-liver ratio was 8.3:1, the tumor-to-muscle ratio was 7.6:1, the tumor-to-blood ratio was 8.4:1, and the tumor-to-kidney ratio was 5:1. Except for the pancreas, which had approximately the same concentration as tumor, there was a tumor-to-nontumor ratio of at least 5:1 in each of the tissues examined.

Other workers (17, 18) have also recognized the tumor specificity of ACPC through tissue distribution studies using the ^{14}C-labeled compound. Studies in the rat and mouse would seem to indicate that labeled ACPC might also be a useful pancreas-scanning agent. However, it has been reported that the pancreas of larger animals, such as rabbits and dogs (19) and Rhesus monkeys (20), does not concentrate ACPC to any significant extent.

We have recently completed a study of the effect of specific activity on the tissue distribution of ^{14}C-labeled ACPC in rats bearing the Morris 5123C hepatoma, and the results are summarized in Table I. No significant difference was observed between the three specific activities used (0.138, 1, and 5 mg/kg)with regard to the relative concentration found in either tumor tissue

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or any of the nine normal tissues exami ..d. Thus specific activity does not seem to be a major consideration in the potential use of ^{11}C-labeled ACPC as a tumor-scanning agent.

Several animal studies by other workers have pointed to the potential value of ^{11}C-labeled tryptophan as a pancreas-scanning agent. In a study of the tissue distribution of all of the common amino acids in the rat at one hour postinjection, Busch et al. (21) found tryptophan to have by far the greatest pancreas specificity. Also Blau and Manske (22) found a very high concentration of ^{14}C-labeled tryptophan in the pancreas of the rat, with 12.5% of the injected dose found in the pancreas at one hour postinjection.

In a study we carried out of the effect of time on the tissue distribution of ^{14}C-labeled DL-tryptophan in the rat (Table II), there was no obvious difference between the tissue concentrations at 30 and 60 minutes postinjection. However, 15 minutes postinjection was apparently not long enough to achieve the high pancreas concentration seen at the longer time periods or to attain a favorable blood clearance. Considering the short half-life of ^{11}C, 30 minutes postinjection would seem to be near the optimum time for a scan to be performed.

A similar study was done on the effect of specific activity on the tissue distribution of labeled DL-tryptophan in the rat at 30 minutes postinjection. A very significant effect was seen with a specific activity of about 0.04 mg/kg giving apparently the most favorable ratios of pancreas concentration to that in other tissues. It should be noted that for the very high specific activity preparation, (0.0004 mg/kg) ^{3}H tryptophan was required. The difference in isotopes could conceivably have led to the lower concentration values for many tissues, particularly pancreas, seen with the high specific activity compound. At any rate the concentration ratios obtained at 0.0004 mg/kg were not as good as those at 0.04 mg/kg. At 1 mg/kg and 5 mg/kg the pancreas concentrations were very similar to that at 0.04 mg/kg. However, the concentration in several other tissues, particularly in the organs of the reticuloendothelial system, were higher at the lower specific activities. Thus specific activity must be a major consideration for labeled DL-tryptophan, with a specific activity of about 0.04 mg/kg apparently giving the best results.

Our results showed under the optimum conditions (specific activity of 0.04 mg/kg and 30 minutes postinjection) a pancreas-to-liver concentration ratio in the rat of approximately 11.5:1. This is compared to an optimum pancreas-to-liver ratio of selenium-75 labeled selenomethionine in the rat (90 minutes post-injection) of only 3:1 (23). Tryptophan labeled with ^{11}C would almost certainly be

preliminary study was carried out on two dogs using a postinjection time of 60 minutes. The results in the two animals were at great variance with each other. In one animal the pancreas-to-liver ratio was 7.6:1; in the other animal, which perhaps coincidentally appeared rather markedly undernourished, the pancreas-to-liver ratio was only 3.7:1. Most of the difference was due to a decreased absolute concentration in the pancreas of the second animal. Further experiments are planned in the dog at both 30 and 60 minutes. We also plan to carry out studies in the marmoset, a primate.

The apparent similarity of fluorine and hydrogen has led to the synthesis and testing of 5- and 6-fluorotryptophan labeled with fluorine-18 as potential pancreas-scanning agents (24). Although the results in rats and mice appeared promising, the pancreas-to-liver ratio in dogs receiving fluorine-18 labeled 6-fluorotryptophan was less than 2:1. Since our pancreas-to-liver ratios in dogs were significantly greater than this, this suggests that the substitution of fluorine for hydrogen does alter the pancreas specificity and decreases the potential value of the compound as a pancreas-scanning agent. The use of tryptophan labeled with ^{11}C would produce no such problems and would be similar to the results which we have achieved in experiments using ^{14}C-labeled tryptophan.

Cyclotron Targetry and Hot Cell Chemistry. The purpose of the cyclotron targetry and associated gas labeling systems is to produce and deliver multicurie quantities of gaseous $^{11}CO_2$ or $H^{11}CN$. These labeled gases are then fed into hot cell chemistry equipment which performs the synthesis and purification of the final ^{11}C radiopharmaceutical product. This section describes the target development leading up to the current level of $^{11}CO_2$ production, the preparations for synthesizing $H^{11}CN$ by two methods, and the progress to date in building and testing hot cell apparatus for the synthesis and purification of ^{11}C-ACPC and ^{11}C-tryptophan. Figures 1A and 1B show the hot cell used in this work.

The first six months of the grant (April through September 1974) were spent designing, procuring materials and equipment, constructing, and obtaining safety committee approval for the target and gas loop systems. Nine experimental runs at the ORNL 86-inch cyclotron were accomplished in the following four months (Oct. 1974 through Jan. 1975). Beam currents varying from 30-170 μA of 22 MeV protons were used for bombardments of 20-60 minutes duration, producing up to 3 Ci of ^{11}C activity in the form of labeled gases. The ^{11}C is produced by internal beam bombardment of a boron oxide (B_2O_3) target assembly. The B_2O_3 (m.p. 450°C) is liquified by the beam and the ^{11}C produced by the ^{11}B (p,n) ^{11}C reaction combines with oxygen in the target. The resulting $^{11}CO_2$ and ^{11}CO diffuses out of the B_2O_3 into a sweep gas which is either recirculated or removed in one pass. Depending on the sweep gas composition and recirculation mode, radiolytic conversion of the $^{11}CO_2/^{11}CO$ mixture to $^{11}CO_2$ or $^{11}CH_4$ can be accomplished.

Figure 2 illustrates the B_2O_3 target material and its support contained in an aluminum capsule tube, which is in turn contained in an aluminum jacket tube. An annulus between the tubes carries cooling water. The 50 mm wide by 6 mm high proton beam is centered on the axis of the tube, and the proton energy is reduced from 22 MeV to 15 MeV in passing through the jacket wall, water annulus, and capsule wall. The target shown in the figure employs 0.25 mm layers of boron oxide fused onto 0.25 mm molybdenum "fins". This design allows a "thick target geometry" beam path to maximize yield, a thin B_2O_3 layer to minimize trapping of the $^{11}CO_2$ and ^{11}CO produced, and maximum heat transfer to permit high beam currents. Due to the extremely small size of the target assembly, difficulties have been encountered in producing the thin dense layers of target material required, and in

Research Plan: Comprehensive Progress Report

devising a technique to accurately adjust the angular position of the target with respect to the beam. We are making rapid progress in solving both these problems, and hope to have accomplished optimum "fin target" performance in two to three months. In addition to the "fin target" work, five target designs employing a fine mesh molybdenum screen to hold the molten target material in place (25) have been evaluated. "Thick target geometry" is easier to accomplish with the "screen target" approach, but trapping of the gaseous activity is a problem and adequate heat transfer provisions are more difficult. Two or more of each of the six different target designs have been constructed and tested in both on-line and recirculating sweep gas modes. Gas compositions have included He, He + 1% O_2, He + 3% O_2, and H_2 + N_2. We anticipate the evaluation of various "fin target" and "screen target" designs to continue for several months.

With the type of targetry described above, we are able to produce approximately 3 curies of $^{11}CO_2$ in gaseous form dispersed in 434 cm^3 of He sweep gas. The activity has been absorbed in a soda lime trap, and a half-life of 20 minutes has been observed for an isolated sample of the gas. There is some gaseous 10 m ^{13}N present at the end of a bombardment from the ^{16}O (p, α) ^{13}N reaction on the oxygen in the B_2O_3 but it will be reduced to negligible levels in the ^{11}C preparation by radioactive decay. We have shown that a reliable long-lasting target can be developed to operate at the very high power densities associated with a 150 µA current of 22 MeV protons (> 3.3 Kw generated in a 1.5 cm^3 volume). We have determined the significant parameters affecting the operation of the targetry and gas loops, and plan to increase the yield of gaseous ^{11}C activity by a factor of two by mid-1975. This can be accomplished through further target development, higher beam current, and experiments designed to optimize the control and shaping of the spatial distribution of the proton beam.

A schematic of the hot cell equipment used for the production of labeled gases is shown in Fig. 3. Continuous monitoring of ^{11}C activity is performed with an air ionization chamber calibrated with ^{85}Sr and ^{137}Cs sources of known absolute activity (produced and measured by the Oak Ridge National Laboratory Isotopes Division). The 514 KeV gamma from 65 d ^{85}Sr provides a close analog to the 511 KeV annihilation photons from 20m ^{11}C, and the 662 KeV gamma from 30y ^{137}Cs provides a convenient long-term standard. On-line, recirculated, or isolated ^{11}C sweep gas activities in the range of 25 µCi to 25 Ci can be measured in a stainless steel vessel of known volume in the well of the ionization chamber.

Equipment for the production of $H^{11}CN$ by two alternate methods was constructed during the period October through December 1974, consisting mainly of the nickel and platinum contact catalysis furnaces indicated in Fig. 3. Figures 4B and 4C indicate a synthetic and a radiolytic scheme for producing $H^{11}CN$. In the synthetic method (26), ^{11}CO and $^{11}CO_2$ in H_2 are passed through a 350°C nickel wool bed to produce $^{11}CH_4$. Gaseous ammonia is then bled in and the resulting $^{11}CH_4$+NH_3+H_2 is passed through a 1000°C platinum wire bed to produce $H^{11}CN$. In the other method (26), we plan to radiolytically convert a mixture of ^{11}CO and $^{11}CO_2$ in H_2/N_2 sweep gas to $^{11}CH_4$ and NH_3. Theoretical calculations and our preliminary cyclotron experiments with H_2/N_2 sweep gas mixtures indicate that a sequence of recirculation and on-line operation will be required to obtain the optimum amount of radiolysis. One-pass on-line operation does not produce enough eV/molecule to convert the $^{11}CO_2/^{11}CO$ to $^{11}CH_4$ and produce NH_3, and recirculation greater than 10 minutes causes the formation of solid polymers which plate out in the gas loop. After optimum recirculation, the sweep gas containing $^{11}CH_4$ and NH_3 will be passed through the 1000°C platinum catalyst to produce the desired $H^{11}CN$ (27). We plan

[redacted]

to evaluate the efficiency of producing $H^{11}CN$ by using a soda line trap prior to the Pt catalyst to remove any unreacted $^{11}CO_2$, and then bubbling the sweep gas containing the $H^{11}CN$ through a flask of strong base in the well of the ionization chamber in order to trap and quantitate it. Any unreacted ^{11}CO would not be trapped. We expect to complete comparison testing of the radiolytic and synthetic methods by mid-1975.

Other work anticipated during the remainder of the first grant year includes instrumentation for continuous strip chart recording of ionization chamber gas activity and of absolute pressure in the gas loop. Replacement of the present sweep gas flow meters with those of better quality and a more accurate calibration is also planned.

An overall goal for the end of the first project year is to have developed the target and gas labeling systems to the point where at least 2 Ci of $H^{11}CN$ has been produced and utilized for preliminary ^{11}C-ACPC and ^{11}C-tryptophan synthesis trials. It may be possible to surpass this goal for $H^{11}CN$ production by a factor of two.

The rapid synthesis and purification techniques developed for ^{11}C-ACPC and ^{11}C-tryptophan using ^{14}C materials were described earlier in the proposal. The following description pertains to equipment required to perform the ^{11}C synthesis steps using the hot cell and manipulators shown in Figs. 1A and 1B. The apparatus designed and built for this purpose is shown by the schematic in Fig. 5 and the photographs in Figs. 6A and 6B. This equipment was designed, built, and tested during the first seven months of the first grant year and is now being utilized for ACPC and tryptophan synthesis trials with ^{14}C materials.

The apparatus consists of a vertical column of three heated stainless steel chambers of approximately 10 ml volume each with transfer valves above, in between, and below. The lower two chambers are instrumented with thermocouples. The upper chamber is a pressure-injection vessel for reagents, and has a gas supply port in the side for this purpose. The center chamber, typically operated at 210°C, has a port at the base for bubbling $H^{11}CN$ through an aqueous solution prior to several reaction steps. The contents are then transferred through the filter to the lower chamber, typically operated at 120°C, for preliminary purification steps. This chamber has an injection port near the top for reagents and a gas supply port near the base for purging. Temperatures in the lower two vessels are controlled by Variacs and monitored by pyrometers mounted in the control box shown in Fig. 6B. The final product containing ^{11}C-ACPC or ^{11}C-tryptophan is then transferred out the bottom of the lower chamber onto a short cation exchange column for purification. Carbon-11 activity eluted off the column is monitored by a shielded probe and strip chart recorder.

After gaining some experience through evaluating and modifying this equipment, it will probably be very useful to duplicate it so that it can be simultaneously used for ^{14}C laboratory studies and ^{11}C production runs. It should prove to be an efficient tool for performing parameter studies necessary to develop fast synthetic techniques for future candidate radiopharmaceuticals. We anticipate that this apparatus will be used in the cyclotron hot cell to produce ^{11}C-ACPC and ^{11}C-tryptophan by approximately May 1975. Procedures will then be developed for routine weekly production and delivery of these radiopharmaceuticals to ORAU facilities for clinical evaluation.

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d. Publications: none

e. Staffing:

Raymond L. Hayes, Senior Scientist, 04/01/74 - present.
Bruce W. Wieland, Scientist, 04/01/74 - present.
Lee C. Washburn, Associate Scientist, 04/01/74 - present.
Thomas A. Butler, Research Staff Member, ORNL Consultant, 04/01/74 - present

B. Specific Aims

The specific aim of this supplemental grant application is to provide for the fabrication of a state of the art positron emission transaxial tomography (PETT) instrument for the coincidence imaging of positron annihilation radiation from ^{11}C-labeled radiopharmaceutical agents that are under development in the parent project (1 RO1 CA 14669). We anticipate that: acquisition of materials and fabrication will require 9 months, prelinical testing will require 3 months, and that the remaining 9 months in the parent grant period will be devoted to full clinical use of the instrument.

C. Methods of Procedure

1. Construction

Basic operation. The positron emission transaxial tomograph (PETT) system we are proposing is very similar to the clinical PETT unit recently completed (Jan. 1975) at the Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri (see Background). The system will consist of 48 NaI (Tl) scintillation detectors arranged in a hexagonal array as shown in Fig. 7 (12). Each opposing bank of eight detectors will be connected in cross coincidence such that the radiation from the subject will be seen as originating from within 8x8 = 64 discrete cylinders passing through the space between all pairs of detectors as shown in Fig. 8 (12). For simplicity, the cylinders of activity henceforth will be referred to as lines of activity.

Two additional sets of opposing detectors will also collect data simultaneously. After sufficient data has been collected, the opposing detectors will translate one cm in the same direction and data is again collected. These one cm steps are continued until five steps have been completed. At this point a total of 64 lines x 5 steps x 3 detector sets = 960 lines of activity have been stored in the computer along with their geometric locations. Next the computer procedure 3° of rotation and the translation process and data collection is repeated. After five steps of translation the detectors are again rotated 3°C. This motion is continued until twenty 3° steps have been taken (a total of 60° of rotation is accomplished). The final data consists of 960 lines x 20 steps = 19,200 discrete lines of activity collected and stored in the computer along with their location. The strength or counting rate of each line is proportional to the activity stored in the tissue along that line.

At this point a reconstruction algorithm using Fourier transforms and noise reducing filter functions is applied by the computer to the 19,200 lines of activity to construct the image in the x, y plane. The results of the reconstruction program produces a single tomograph of a transaxial slice through the sample approximately

one cm thick. Figure 9A (12) represents the 3-dimensional view of the tissue with a slice ΔX in the thickness being considered. Figure 9B (12) shows three sets of lines from the 19,200 total lines. The two hot spots are shown dark compared to the white cold spot (absence of activity). Also plotted in Fig. 9B is the counting rate versus distance across the scan showing peaks in each set of lines that pass through the hot spots and a minor valley at the cold spot location.

The rather massive redundancy of many different lines passing through the same activity, but at different angles, improves both the resolution and contrast. The final tomograph is shown in Fig. 9C (12).

After reconstructing the image in the x, y plane the data is placed on an oscilloscope face at the same relative location as the original activity stored in the ΔX slice. The intensity of the oscilloscope beam is proportional to the activity stored in the tissue, thus forming the final image of this particular slice. If the subject is moved through the detectors axially and the process repeated, additional scans can be produced.

The mechanical construction of the proposed PETT system will be very similar to the prototype recently completed at the Washington University School of Medicine, St. Louis, Mo. The pictures taken of the PETT system at St. Louis are shown in Figs. 10 through 13, and provide an indication of how the construction will be done and what the finished machine will look like with the covers removed for servicing.

Materials and timing. The timing and personnel diagram shown in Fig. 14 is an estimate of the work flow and personnel requirements to build and test the PETT instrument. Work is assumed to start July 1, 1975, on the mechanical system and continue for six months. All mechanical fabrication and assembly will be done in the existing ORAU shops. The estimated cost is:

Raw material	$3,000
Motors, gears and drives	7,000
Encoders	3,000
Labor and overhead	30,000
Total	$43,000

It is anticipated that the electronics, including the computer, will go out for bids on approximately July 1, 1975, and work will start on October 1, 1975, and be finished six months later. A detailed cost breakdown for the lowest of two proposals received for the electronic equipment (see page 4) is listed below:

Tennelec Inc., Oak Ridge, Tenn.

Quantity	Description	Unit Cost	Total Cost
48	Preamplifier, Model TC155A	$ 200	$ 9,600
48	Amplifier, Model TC211M	240	11,520
48	Cross-over pickoff, Model TC446M	380	18,240
12	H.V. supply, Model TC940A	460	5,520
12	H.V. Dist. box, Model TC880	250	3,000
12	NIM bin and power supply, Model TB-3/TC911	575	6,900
48	12' H.V. cable	30	1,440
48	12' signal cable	8	384

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96	2' signal cable	$ 6	$ 576
3	Coincidence and scaler modules	2,333	7,000
7	Motor drives	714	5,000
48	Detectors	369	17,712
1	Ramtec display	15,040	15,040
1	Movable head disc drive	12,000	12,000
1	Interdata computer, 32 K fixed-point CPU	35,146	35,146
3	Cabinets	87	260
			$ 149,338

Combining the mechanical and electronic costs the total equipment price is $192,338. Again referring to Fig. 14, 9 months after funding the instrument is projected to be complete and ready for preclinical testing. Clinical trial will commence 3 months later.

ORAU's professional instrument shop, under the direction of a project engineer (see biographical sketch of R. R. Feezell), will provide services for construction of the electromechanical portion of the PETT system. However, since it was not considered feasible for ORAU to construct and integrate completely on its own the electronic portion of the PETT instrument (see p. 5), we will necessarily make provisions for the inclusion of expert electronics personnel services in all electronics bids. It is our present understanding that both Tennelec Inc., and ORTEC Inc., have included in their preliminary bids to us the following services: (1) the specification of requirements and purchase and inspection of all standard electronic hardware; (2) carrying out detailed design and fabrication of all electronics which are not standard models with all circuits internal to the electronic system being guaranteed to be compatible; and (3) assembling all electronic components into suitable enclosures and providing technical personnel for integration and overall systems check out. We will have available to us the cooperation and advice of the originators of the PETT system (see section on "collaboration"). When desired we can also obtain assistance from the instrumentation groups at ORNL with whom we have collaborated for many years.

2. Testing

After the electronic assembly has been completed and tested, it will be connected to the mechanical system and the computer control program then tested for proper operation of the translation and rotation movements.

The length of the counting cycle to obtain good statistical results must be determined for each general study. However, a maximum singles counting rate of 50,000 c/s will be used to obtain the coincidence loss rate.

The resolving power will be tested by making scans of line sources with progressively closer line spacings to determine the final limit of the resolving power. To test for contrast rendition, a relatively larger amount of activity of known geometry will be placed inside a vessel containing a larger amount of material, but weaker in activity. Successive scans can be made as the ratio of the two activities are reduced to the point where the known geometry sample can no longer be discerned. This ratio will be the lower limit for discernible contrast.

At this point we will then optimize the noise reducing filter function. Since the filter is a compromise between reduction of random noise inherent in any electronic system and the loss of useful information, an optimum function should be

Research Plan: Methods of Procedure

realizable. Specifically a filter function will be chosen based on intuition and experience, the resolution and contrast tests will be run, the filter function will be changed, the tests repeated, and results compared and in this way a "best" filter function can be found.

3. Clinical Use

Clinical studies. Protocols for clinical studies will be developed for each ^{11}C-labeled compound that has been found in animal tests to be promising for diagnostic use and free of untoward or toxic effects. These tests will be carried out at the ORAU Medical Division facilities in Oak Ridge. The patients will come from the Oak Ridge Hospital (a short block away), from Knoxville hospitals, or other referring physicians or institutions. A referral base is available through institutions associated with ORAU and the Cooperative Group to Study Localization of Radiopharmaceuticals. Ambulatory patients can come from considerable distances if necessary; seriously ill patients from the nearby population can be transported by ambulance if necessary. The East Tennessee Cancer Research Center (ETCRC), of which ORAU is a founding member, has indicated interest and support for this project and also their intent to help supply patients. The Medical Division has a long history of cooperation with referring physicians and the ability to attract patients for experimental work. Although normal volunteers will not be used for these studies, suitable control subjects will be available from those patient volunteers with cancer that have been shown by clinical and laboratory tests to be normal with respect to the organ or function under investigation.

The PETT instrument will not have its greatest usefulness in patients with widely disseminated occult malignancy, but rather in those with questionable or known lesions in a limited area of the body, about which maximum localization information is needed for planning therapy. Preliminary rectilinear scans and positron camera images will be used to identify discrete areas for the PETT studies.

Each new ^{11}C-labeled compound will require its own protocol for human study. The two compounds currently on the agenda for study, ^{11}C-labeled tryptophan and ACPC (see progress report), will be studied from the point of view of estimating more accurately the internal absorbed radiation dose and optimum scanning conditions. These studies will include both assays for determining blood clearance, and urinary excretion. In some instances the ^{11}C-labeled agents may be given just before a biopsy or operation so that tissue assays can be obtained. To evaluate abnormalities shown by the ^{11}C studies, correlations will be sought by means of radiologic tests, clinical and laboratory procedures, and surgical confirmation. In fatal cases ultimate diagnoses will be further established by autopsy.

As a potential pancreas-scanning agent, ^{11}C tryptophan will first be studied in patients whose cancer is in some other part of the body and who have no pancreatic disease. Repeated scans will be made using an Ohio Nuclear rectilinear scanner modified for the detection of positron annihilation radiation, and the PETT device. Successful outcome of these studies will be followed by a study on patients with known or suspected cancer of the pancreas to test both the ^{11}C tryptophan preparation and the PETT instrument. These studies will be carried out in cooperation with the oncology services of the other member institutions in the ETCRC.

Carbon-11 ACPC being a potentially general tumor-scanning agent will be tested on patients with known solid tumors. The study will involve sequential rapid whole-body or torso scans on the modified Ohio Nuclear whole-body rectilinear scanner

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to identify areas of concern. Suspicious areas will then be studied in detail with the PETT device. With successful conclusion of these studies, an evaluation of ^{11}C ACPC with other tumor-scanning agents, e.g., ^{67}Ga, should be undertaken.

Other potential ^{11}C-labeled agents for use with the PETT system that are presently under consideration are estradiol, thymidine, ethidium bromide, and hyaluronidase. Positron-emitting agents other than ^{11}C can of course also be imaged with the PETT instrument.

Ethical and formal requirements. Each new labeled compound will be presented to our Committee for Use of Radioisotopes in Humans, as well as the ORAU Committee on Human Studies. We hold jointly with the Oak Ridge National Laboratory a general institutional assurance, dated March 2, 1972, and are in compliance with the requirements in DHEW Grants, Administration Manual Chapter 1-40, effective April 15, 1971. We are familiar with the requirements of the Food and Drug Administration and will submit an IND (Investigational New Drug) Form for each new compound.

Radiopharmaceutical control. The Medical Division of ORAU has a well-established program for the development and testing of new radiopharmaceuticals. This includes the USP standard pyrogen testing procedure using preconditioned rabbits. In view of the short half-life of ^{11}C, the USP safety of labeled materials will have to be based on tests done on previous batches made with the same reagents and handled under the same conditions as those that are administered. We will, however, make use of the more rapid limulus technique on each batch of ^{11}C-labeled material. A newly remodeled clean room with laminar flow facilities is available for handling materials to be administered to humans.

D. Significance

The work projected in parent grant 1 R01 CA 14669 is expected to considerably broaden the capabilities for detection of cancer. There is great potential inherent in organic and biological compounds labeled with ^{11}C as agents for external visualization of tumors and specific organs. The high spatial resolution offered by use of a positron emission transaxial tomography device (PETT) will make it possible for us to delineate much smaller malignant lesions and anatomical structures than is possible with current imaging devices. Combining highly promising ^{11}C radiopharmaceutical technology with this exciting new development in imaging instrumentation should produce results that will greatly augment the armamentarium of the clinical diagnostician. A major advance in nuclear medicine that will be comparable in significance to that produced by the combination of the Anger camera with ^{99m}Tc would not be surprising.

Our proposed use of the PETT system in our program will considerably enhance the clinical development of this important new instrument. The specific ways in which ORAU can contribute are the following: (1) by developing a somewhat improved version of the PETT device through use of the resources of the technical instrument companies and the general expertise available in the Oak Ridge area and through subsequent clinical testing, we expect to hasten the movement of the instrument into the private sector so that its benefits can be extended at an early date to cancer patients in general; (2) by utilizing the instrument to test new ^{11}C-labeled compounds that at present can only be prepared at Oak Ridge because of ORNL's capacity to produce large quantities of ^{11}C, we will in all probability develop new

Research Plan: Significance

proof of their clinical usefulness such compounds might then be made generally available at other ^{11}C installations through subsequent improvements in methods of synthesis and thus hasten the general use of the PETT system; (3) we can also carry out clinical PETT tests with ^{11}C-labeled compounds and other agents not requiring the Oak Ridge high yield ^{11}C production facility, but which so far are only being developed in Oak Ridge; and (4) by maintaining close contact with Ter-Pogossian's group at St. Louis, and thus helping to confirm or question each other's results, we would provide mutual assistance and in turn speed movement of the PETT system into general use. The ultimate result of our use of the PETT system is, therefore, expected to be earlier diagnosis and more accurate staging of cancer, with better cure rates in some cases and improved palliation in others.

E. Facilities Available

At the present time the ORAU Medical Division maintains a well-equipped nuclear medicine facility for studying outpatients. The equipment includes a variety of imaging devices, probe counters, whole-body counters, dose calculators, automatic well counters, and patient areas for administering and attending to the needs of the patients. A clean room with laminar flow hoods is also available for the preparation of radiopharmaceuticals. A scintillation camera equipped with a positron-detection device is available for imaging low levels of ^{11}C. We also have a modified dual probe Ohio Nuclear whole-body scanner with coincidence counting capability. This scanner is interfaced through a PDP 11/20 buffer to an IBM 1800 on-line computer for purposes of data processing.

We anticipate an eventual merger of the nuclear medicine program at ORAU with the East Tennessee Cancer Research Center. As this merger takes place the ORAU facilities will be moved at least in part to Knoxville. Because of the short half-life of ^{11}C and other similar radionuclides together with problems related to the transportation of such materials from Oak Ridge to Knoxville, some of the ORAU facility will probably be retained in Oak Ridge, either in the present location or at a site nearer the ORNL 86-inch cyclotron.

ORAU maintains a highly-equipped instrument shop staffed with personnel having extensive and long-term experience in electronics and instrument fabrication.

The PETT system will be located in a self-contained room (see alterations) and will as a result be isolated from distractions due to movement of individuals.

F. Collaboration

An excellent collaborative atomosphere exists between the originators of the PETT system at the Washington University School of Medicine in St. Louis and the Radiopharmaceutical Development Group of the ORAU Medical Division. B. W. Wieland of ORAU completed a 2-1/2 year dissertation research project in Dr. Ter-Pogossian's Division of Radiation Sciences at The Edward Mallinckrodt Institute of Radiology in September 1973. Studies leading to the PETT concept were in progress at that time, and Wieland has been following the project with interest ever since, making periodic visits to Washington University. Dr. Ter-Pogossian has been very helpful in providing information on experimental results and details on PETT system hardware. Dr. Ter-Pogossian has indicated he will continue to do so if this supplement is funded, and will provide copies of computer programs and finished detailed drawings of the mechanical system when necessary. We expect a continuing association with his group during the clinical phase for the PETT system. Should the reviewers wish to

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contact Dr. Ter-Pogossian, he can be reached by telephone at 314-367-6400, ext. 3596 (FTS number). We also have available to us the assistance of the instrumentation groups at ORNL with whom we have collaborated for many years.

Use of Energy Research and Development Administration (ERDA) Facilities and ERDA Contract Requirements:

This research grant application includes a segment of activity which would be performed in facilities of ERDA and governed by an existing contract between Oak Ridge Associated Universities (ORAU) and the ERDA. The ERDA has reviewed this proposal and has concurred in ORAU conducting the described work in the ERDA facilities made available for biomedical research, subject to payment to the ERDA by ORAU from NIH funds of the applicable direct and indirect cost of the work (not including any charge for the use of ERDA facilities) as determined by the provisions of ERDA's contract with ORAU.

It is believed that in large measure the requirements of the ERDA contract parallel conditions which NIH ordinarily applies to its grants. In the event of differences between NIH grant terms and the ERDA contract terms, ORAU is agreeable to meeting both to the extent that they are not in conflict, and to applying those most favorable to the United States Government where this is involved. If NIH is aware of problems which such an approach would produce or suggest, ORAU upon receipt of such advice would refer the matter to the ERDA for direct resolution with NIH.

By way of general information, ORAU's contract with the ERDA is a cost-type contract financed under a Government-fund account. The specific contract work is formulated in cooperation with the ERDA and authorized within general guidelines in the contract. Contract terms include ERDA responsibility for Government ownership and control of inventions, data, and other research products. Ownership of all equipment and facilities acquired by ORAU with ERDA funds is vested in the U. S. Government at the time of acquisition. The contract also contains all the terms generally common to Government contracts of the type under which ORAU conducts research operations in Government-owned facilities.

G. Principal Investigator Assurance

"The undersigned agrees to accept responsibility for the scientific and technical conduct of the research project and for provision of required progress reports if a grant is awarded as the result of this application.

01/31/75
Date

Raymond L. Hayes
Raymond L. Hayes
Principal Investigator"

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TABLE I

Effect of Specific Activity on the Tissue Distribution of ^{14}C-Labeled ACPC in Rats Bearing the Morris 5123C Hepatoma at 30 Minutes Postinjection

Tissue	Percent/g/250g[a]		
	0.138 mg/kg	1 mg/kg	5 mg/kg
Liver	0.489 ± 0.024	0.460 ± 0.034	0.397 ± 0.025
Spleen	0.573 ± 0.023	0.545 ± 0.029	0.470 ± 0.024
Kidney	0.621 ± 0.019	0.603 ± 0.021	0.554 ± 0.021
Lung	0.517 ± 0.012	0.488 ± 0.017	0.425 ± 0.014
Muscle	0.492 ± 0.018	0.472 ± 0.023	0.410 ± 0.008
Bone marrow	0.646 ± 0.024	0.607 ± 0.022	0.544 ± 0.012
Blood	0.508 ± 0.021	0.439 ± 0.022	0.450 ± 0.062
Small intestine	0.854 ± 0.147	0.981 ± 0.120	0.676 ± 0.128
Pancreas	3.210 ± 0.178	3.840 ± 0.129	2.900 ± 0.077
Tumor	1.824 ± 0.053	1.870 ± 0.107	1.989 ± 0.060

[a] Average of 4 animals per group; normalized to a body weight of 250 g.

TABLE II

Effect of Time on the Tissue Distribution of DL-Tryptophan [side chain-3-^{14}C] (0.04 mg/kg) in the Rat

Tissue	Percent/g/250g[a]		
	15 min	30 min	60 min
Liver	1.050 ± 0.036	1.080 ± 0.017	0.960 ± 0.034
Spleen	0.685 ± 0.042	0.766 ± 0.030	0.664 ± 0.010
Kidney	1.630 ± 0.089	1.500 ± 0.035	1.360 ± 0.139
Lung	0.524 ± 0.011	0.489 ± 0.010	0.424 ± 0.006
Muscle	0.248 ± 0.006	0.239 ± 0.000	0.203 ± 0.008
Bone marrow	1.640 ± 0.029	1.750 ± 0.300	1.680 ± 0.344
Blood	0.502 ± 0.050	0.283 ± 0.010	0.257 ± 0.023
Small intestine	1.220 ± 0.035	1.470 ± 0.030	1.330 ± 0.066
Pancreas	8.880 ± 0.028	12.370 ± 0.247	11.840 ± 0.645

[a] Average of 4 animals per group; normalized to a body weight of 250 g.

TABLE III

Tissue Distribution of DL-Tryptophan [side chain-3-^{14}C] (0.02 mg/kg) in the Rabbit at 30 Minutes Postinjection

Tissue	Percent/g/2.5 kg[a]
Liver	0.108 ± 0.000
Spleen	0.125 ± 0.008
Kidney	0.186 ± 0.010
Lung	0.0903 ± 0.007
Muscle	0.0365 ± 0.000
Bone marrow	0.0792 ± 0.000
Blood	0.0625 ± 0.004
Small intestine	0.162 ± 0.006
Thymus	0.0658 ± 0.008
Adrenal	0.105 ± 0.008
Urine	0.363 ± 0.124
Pancreas	0.583 ± 0.032

[a] Average of 4 animals per group; normalized to a body weight of 2.5 kg.

TABLE IV

Tissue Distribution of DL-Tryptophan [side chain-3-^{14}C] (0.04 mg/kg) in the Dog at 30 Minutes Postinjection

Tissue	Percent/g/10 kg[a]	Percent total organ
Liver	0.0310	12.61
Spleen	0.0190	0.86
Kidney	0.0292	2.27
Lung	0.0140	1.36
Muscle	0.0069	-
Bone marrow	0.0164	-
Blood	0.0100	7.0 [b]
Small intestine	0.0257	-
Thymus	0.0286	0.38
Adrenal	0.0221	-
Heart	0.0109	0.64
Pancreas	0.1580	4.92
Urine	-	3.13

[a] Average of 2 animals; normalized to a body weight of 10 kg.

[b] Assuming 7% of total weight to be blood.

FIGURES

Fig. 1A Hot cell located at the ORNL 86-inch cyclontron facility.

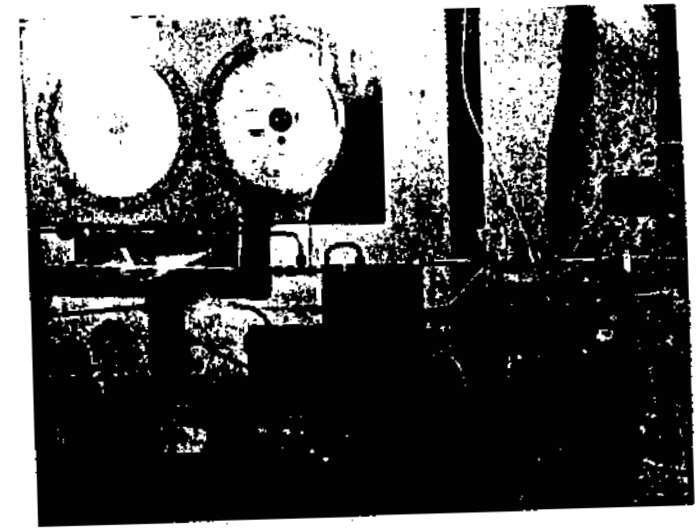

Fig. 1B View through hot cell window showing gas loops and instrumentation used in production and measurement of multicurie quantities of ^{11}C.

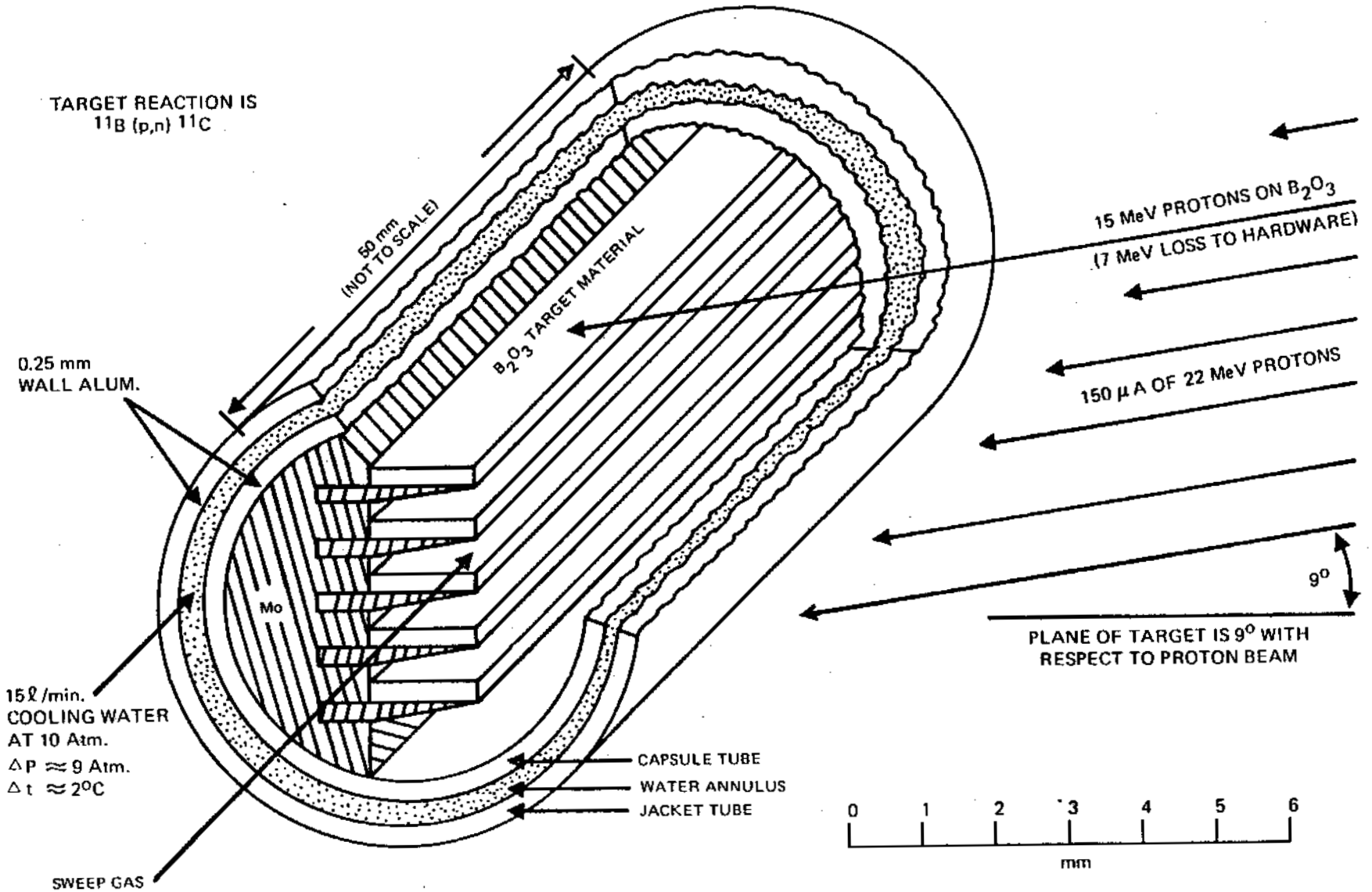

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FIG. 2 CYCLOTRON TARGET SHOWING BORON OXIDE FUSED TO SURFACE OF MOLYBDENUM FINS

[redacted]

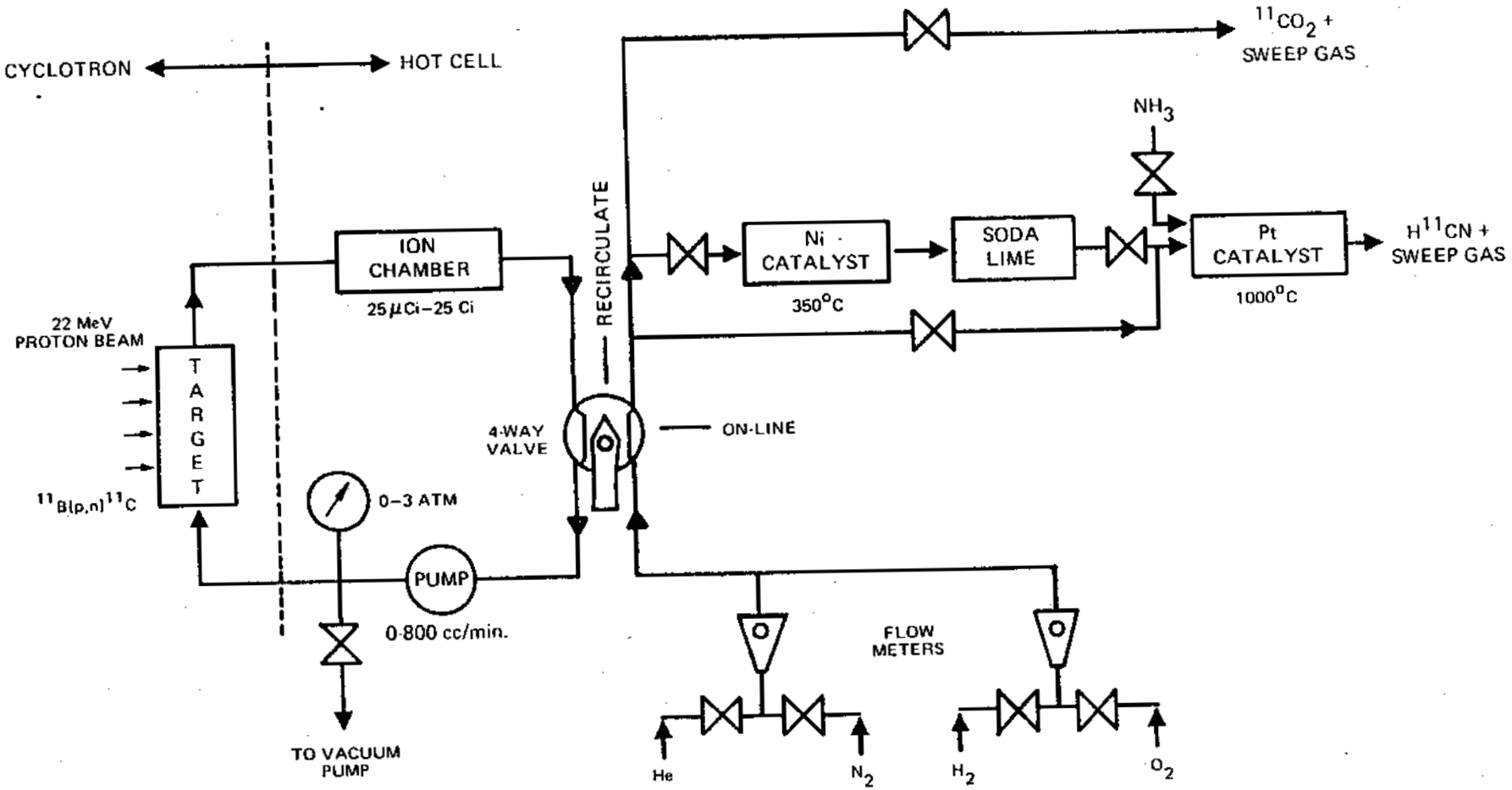

FIG. 3 SCHEMATIC OF HOT CELL EQUIPMENT USED FOR THE PRODUCTION OF LABELED GASES

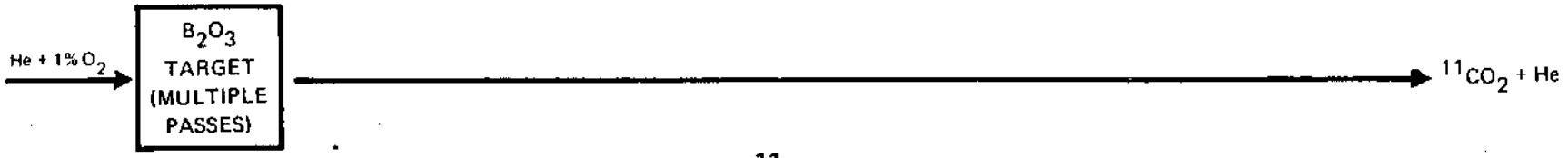

FIG. 4A $^{11}CO_2$ PRODUCTION

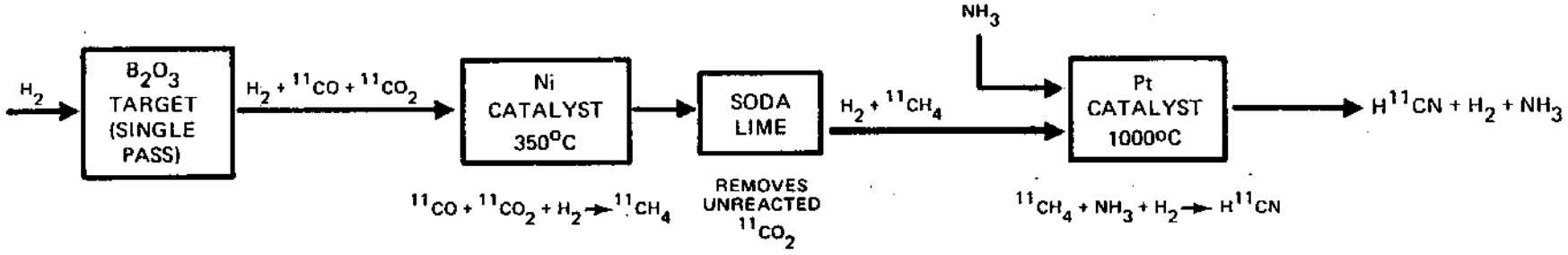

FIG 4B $H^{11}CN$ PRODUCTION-SYNTHETIC METHOD

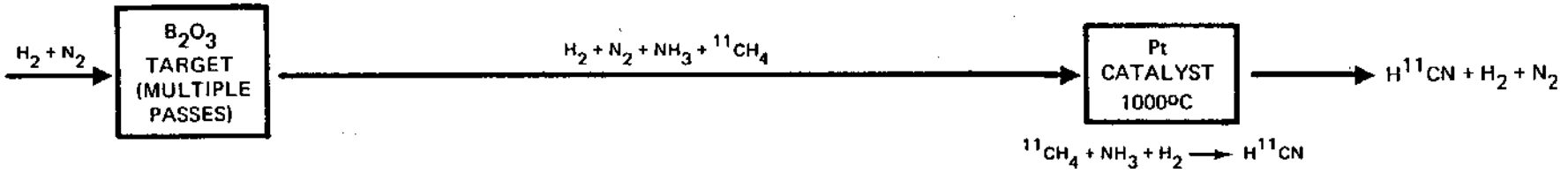

FIG. 4C $H^{11}CN$ PRODUCTION-RADIOLYTIC METHOD

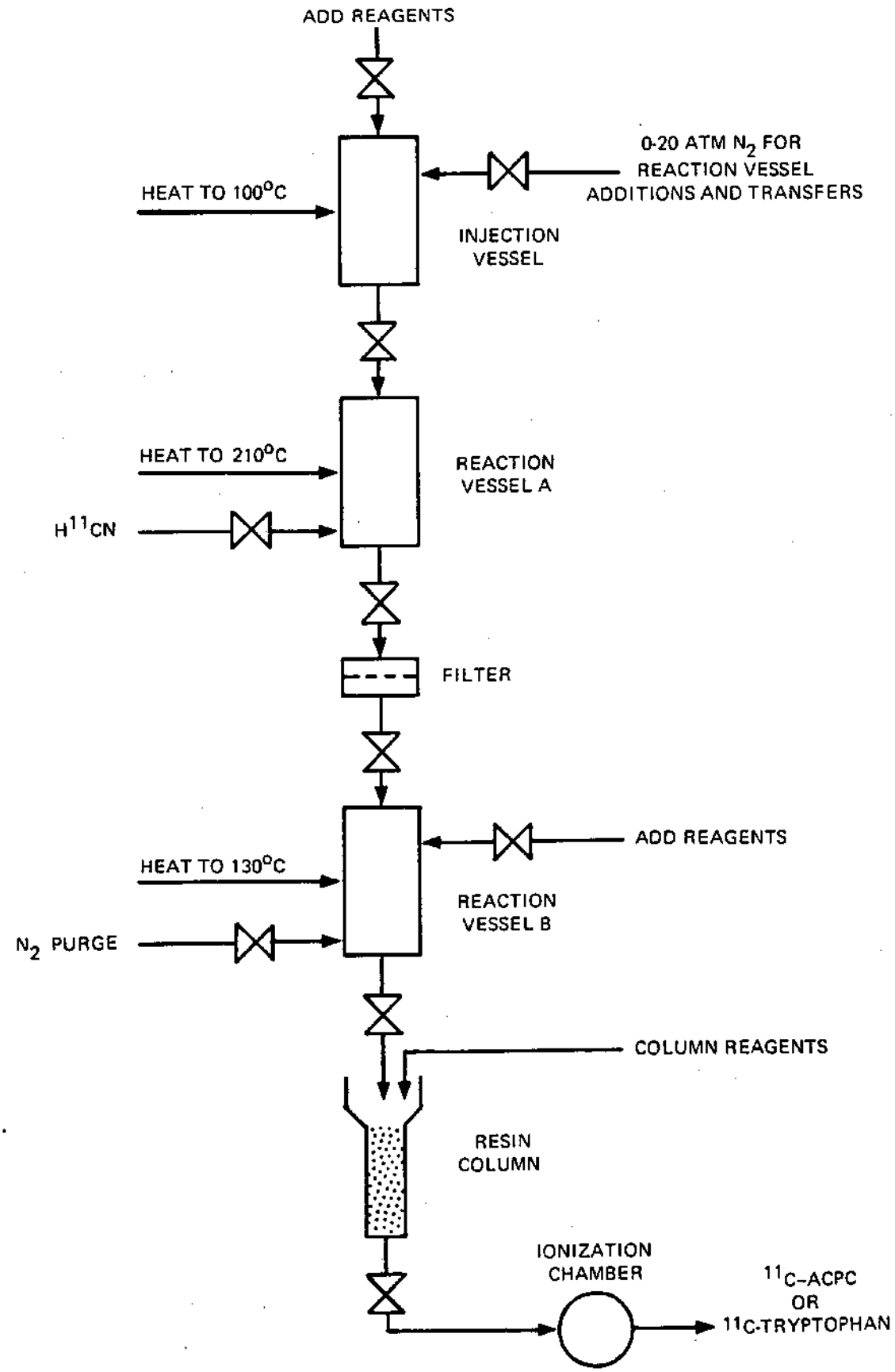

FIG. 5 HOT CELL APPARATUS FOR THE SYNTHESIS AND PURIFICATION OF ^{11}C-ACPC AND ^{11}C-TRYPTOPHAN

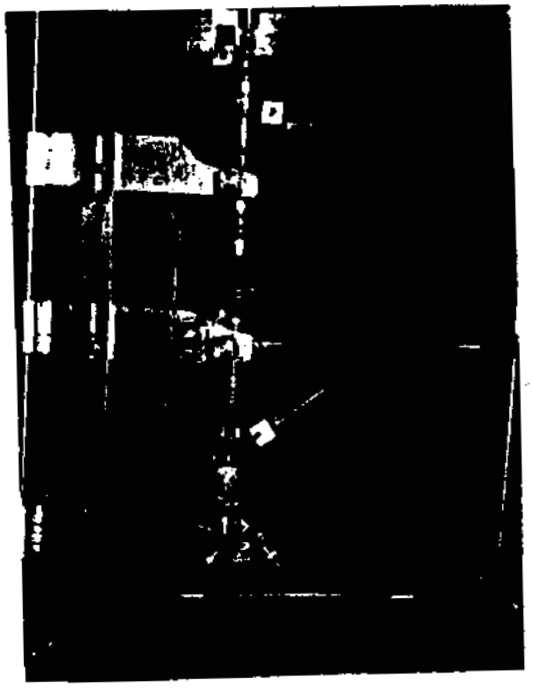

Fig. 6A Hot cell chemistry equipment for the synthesis of ^{11}C-ACPC and ^{11}C-tryptophan starting with H^{11}CN.

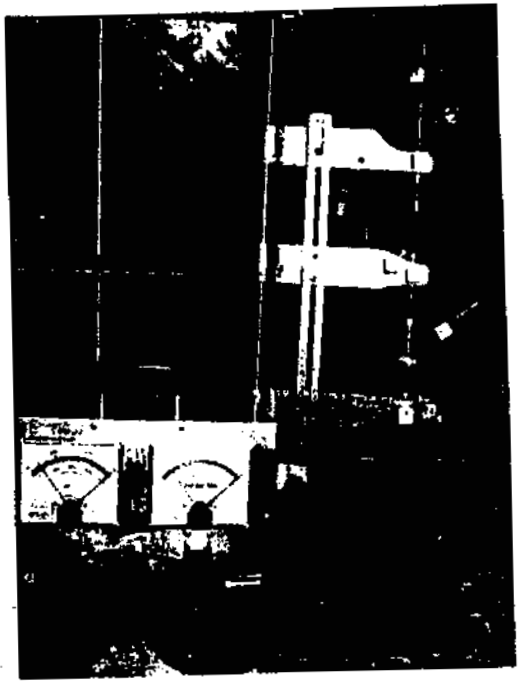

Fig. 6B Hot cell chemistry equipment with instrumentation for controlling and monitoring temperature of two lower reaction vessels.

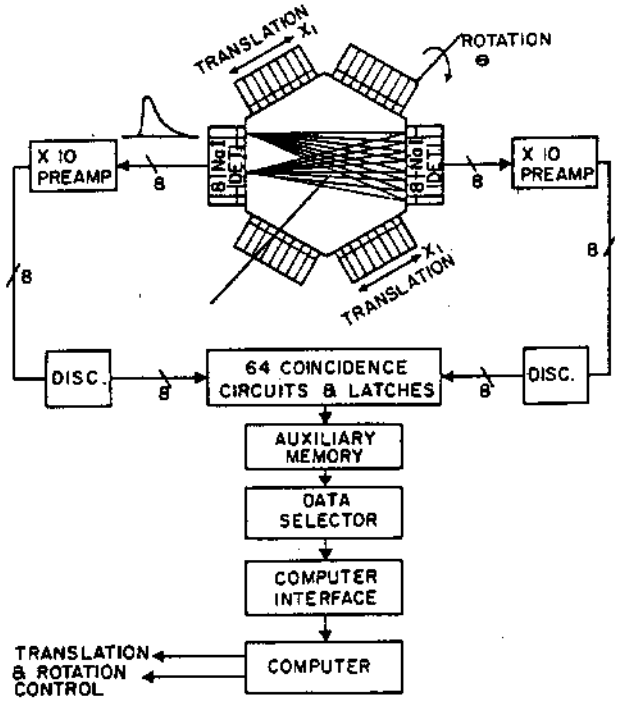

Fig. 7 Simplified block diagram of PETT system showing one of three sets of electronics.

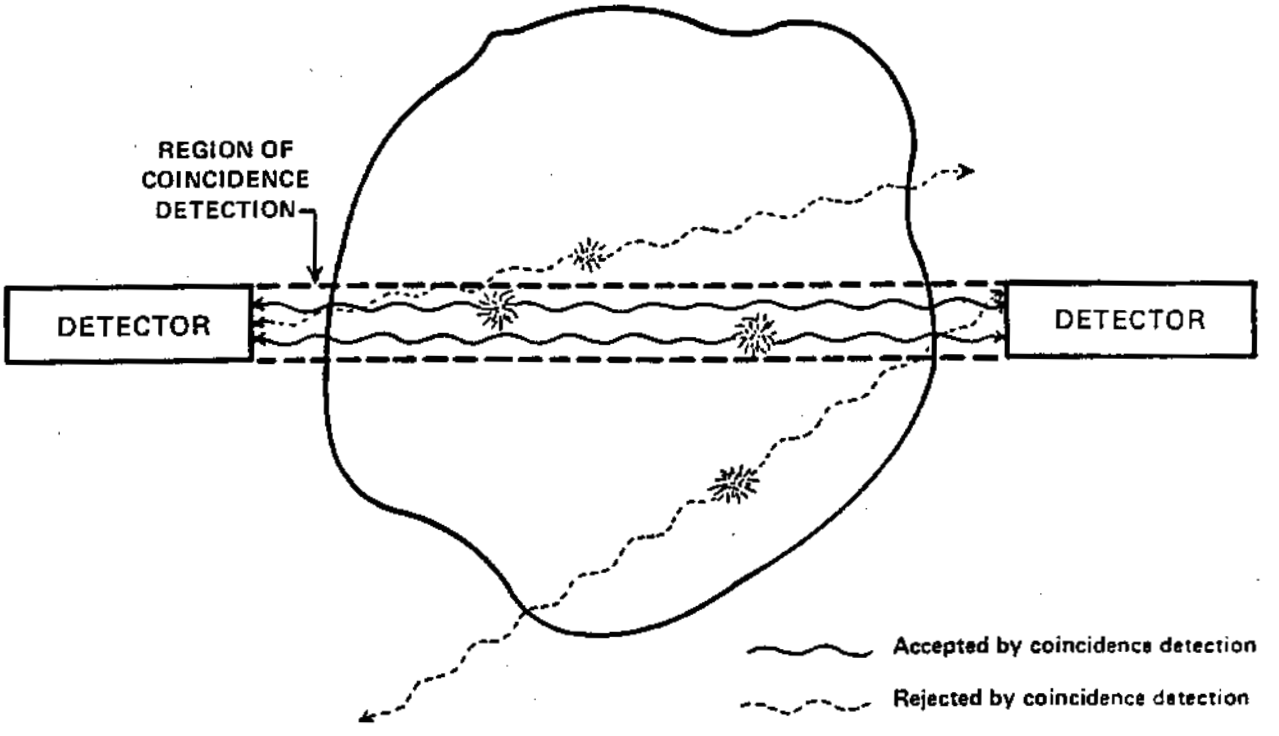

Fig. 8 "Electronic" collimation used in annihilation coincidence detection. Events are recorded only when two 511 KeV photons emitted at 180° following positron annihilation are detected simultaneously.

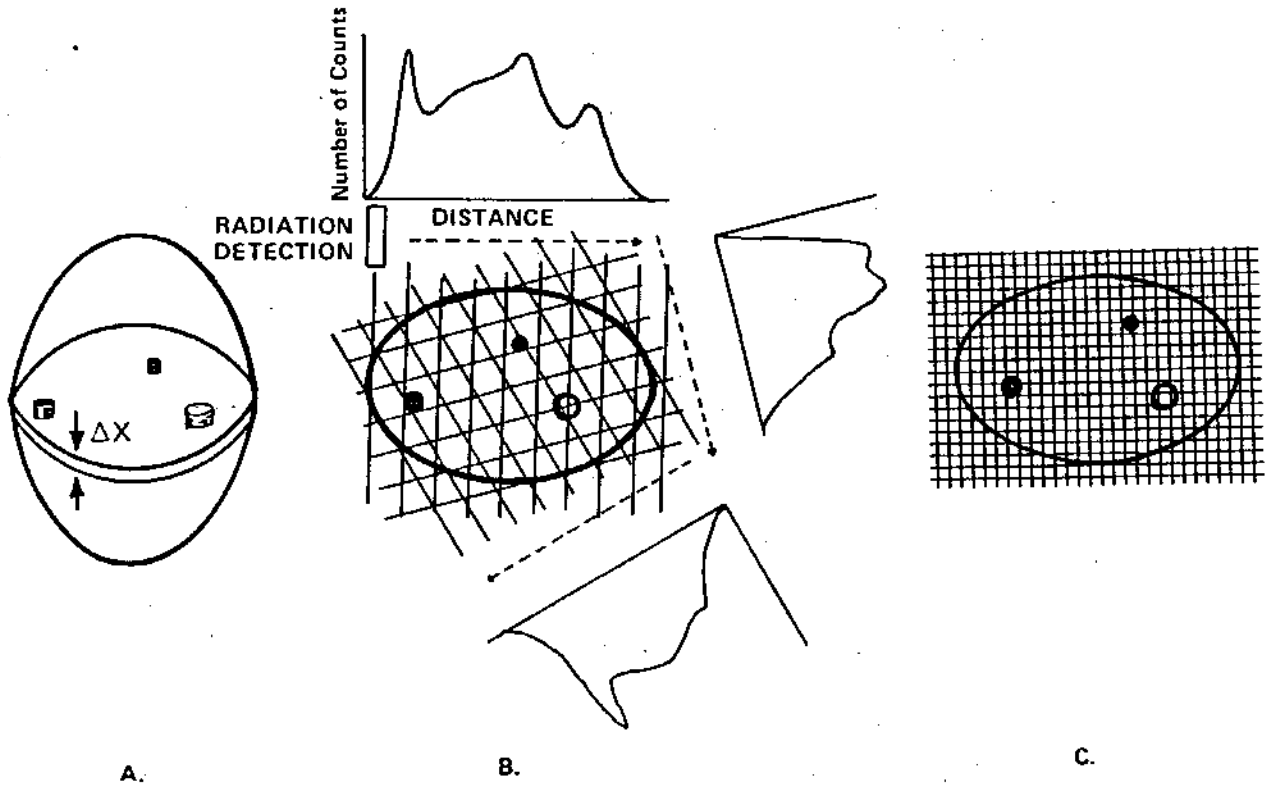

Fig. 9. A. Distribution of activity in cross-sectional slice of three-dimensional object. B. Rectilinear scans performed at a number of discrete angles around cross section of interest. Recorded data consists of activity profiles. C. Reconstructed image formed by using data from activity profiles to mathematically solve for each element in grid or matrix representation.

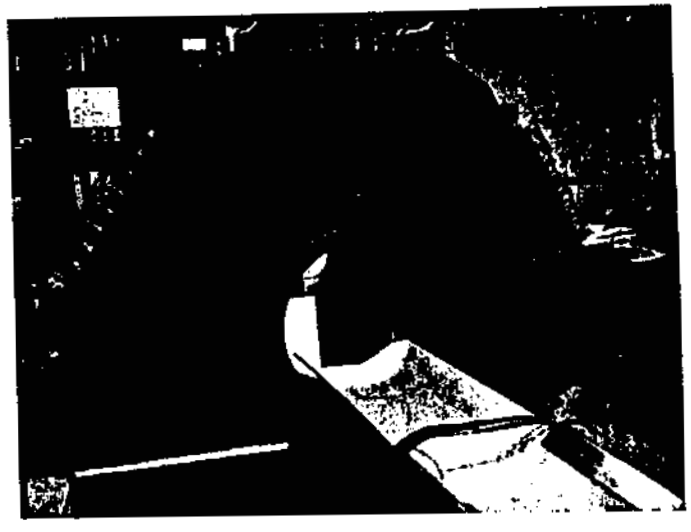

Fig. 10 Rear view of the prototype PETT system showing three of the eight, detector banks, patient table, and some of the framing.

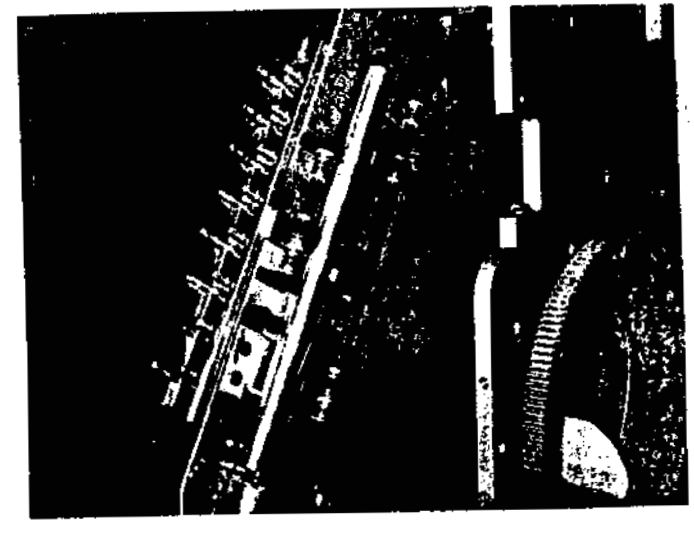

Fig. 11 Close-up of one detector bank showing the lead screw and drive motor for translation in the X_1 direction.

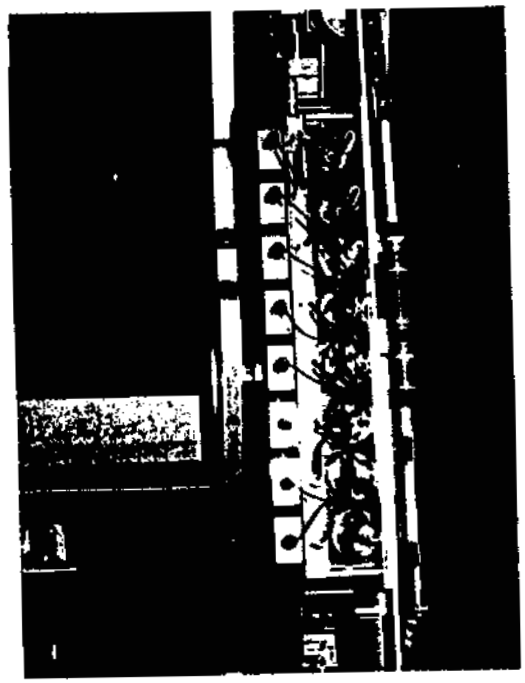

Fig. 12 Close-up side view showing one set of eight detectors and their associated preamplifiers.

Fig.13 Front view showing a patient in place for a chest scan. Also the ring gear and drive motor for rotation in the Θ direction can be seen.

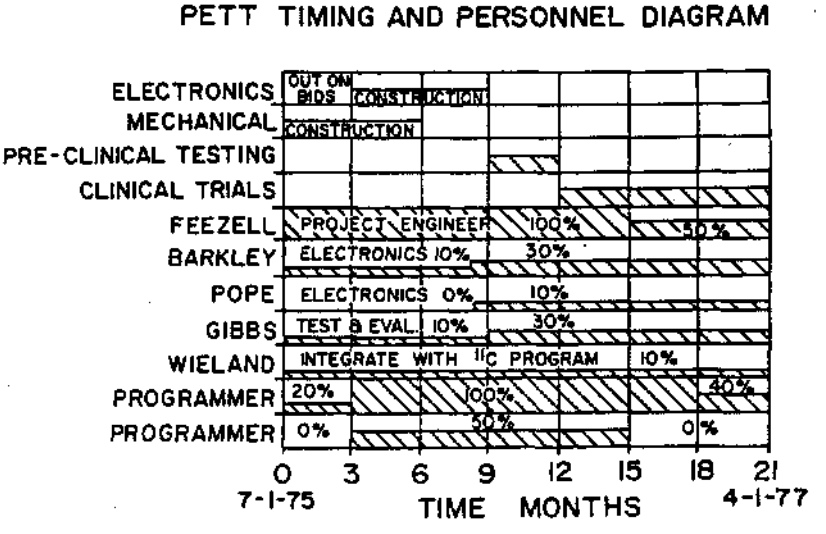

Fig. 14 Provides an estimate of the timing and personnel requirements to build and test the PETT instrument.