





Oak Ridge  
 Associated Post Office Box 117  
 Universities Oak Ridge, Tennessee 37830

July 13, 1982

Dr. William R. Bibb, Acting Director  
 Energy Programs and Support Division  
 Department of Energy  
 Oak Ridge, Tennessee 37830

Subject: NIH RENEWAL GRANT NO. 5 R26 CA29490-02, "C-11-AMINO ACIDS/POSITRON  
 ECT FOR PANCREATIC STUDIES"

Dear Dr. Bibb:

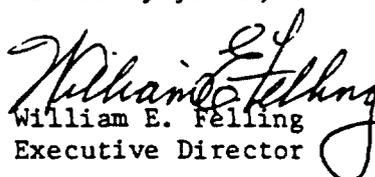
The subject renewal grant in the amount of \$76,376 plus applicable indirect costs has been awarded to ORAU by NIH. This work will continue under the direction of Dr. Karl F. Hubner and will be carried out at the Medical Division in DOE owned facilities.

Personnel to be assigned to this grant will be as follows:

<u>Name</u>	<u>Percent of Time</u>
Karl F. Hubner	20%
William D. Gibbs	20%
Lee C. Washburn	10%
Anita Forester	50%

At the close of each accounting period, ORAU will reimburse the DOE contract account for all applicable direct and indirect costs. Your approval is requested to continue this project as work under Contract DE-AC05-76OR00033.

Sincerely yours,

  
 William E. Felling  
 Executive Director

COUNTISS:psr  
 Enclosure

1079301

2081-80  
 R 4261

DATE ISSUED: JUN 16 1982

**NOTICE OF GRANT AWARD**

GRANT NUMBER:  
 5 R26 CA29490-02 SRC

TYPE OF AWARD: NATIONAL ORGAN SITE PROJECT  
 AUTHORIZED BY: 42 USC 241 42 CFR 52

TOTAL PROJECT PERIOD:  
 From 07/01/81 Through 06/30/84

AWARDED BY:  
 NATIONAL CANCER INSTITUTE

Title of Project or Area of Training  
 C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES

Grantee Institution OAK RIDGE ASSOCIATED UNIVERSITIES P O BOX 117 OAK RIDGE, TENN 37830	Principal Investigator/Program Director/Awardee HUBNER, KARL F MD OAK RIDGE ASSOCIATED UNIV P O BOX 117 OAK RIDGE, TENN 37830
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APPROVED BUDGET	
FOR BUDGET PERIOD 07/01/82 Through 06/30/83	
Salaries and Wages . . . . \$	35,562
Fringe Benefits . . . . .	7,686
<b>Total Personnel Costs . . . . .</b>	<b>\$ 43,248</b>
Consultant Costs . . . . .	3,800
Equipment . . . . .	
Supplies . . . . .	4,400
Travel - Domestic . . . . .	1,700
- Foreign . . . . .	
Patient Care - Inpatient . . . . .	
- Outpatient . . . . .	1,500
Alterations and Renovations . . . . .	
Contractual or Third Party Costs . . . . .	
Other . . . . .	21,728
Trainee Stipends . . . . .	
Trainee Tuition and Fees . . . . .	
Trainee Travel . . . . .	
<b>TOTAL DIRECT COSTS</b> →	<b>\$ 76,376</b>

AWARD COMPUTATION	
1. DIRECT COSTS . . . . .	\$ 76,376
2. INDIRECT COSTS . . . . .	0
(Calculated at _____ rate)	
3. TOTAL . . . . .	\$ 76,376
4. Less Unobligated Balance From Prior Budget Period(s) . . . . .	\$
5. AMOUNT OF THIS AWARD →	\$ 76,376

COST SHARING CONTRIBUTION	(1) Per Instl. agreement dated 01/01/73
	(2) Per Indiv. agreement, minimum
SUPPORT RECOMMENDED FOR REMAINDER OF PROJECT PERIOD*	
Budget Period	Total Direct Costs (Includes Stipends)
03	84,098
04	NONE

When PHS Prior Approval is required for rebudgeting, submit request to Grants Management Official below. #SEE REMARKS

\*Subject to availability of funds and satisfactory progress.

REMARKS:  
 APPLICABLE INDIRECT COSTS WILL BE PROVIDED ON A SUMMARY NOTICE.  
 REFER TO ADDITIONAL TERMS AND CONDITIONS OF AWARD.

#GRANTS MANAGEMENT CONTACT: MS. KATHERINE SEIKEL *LS* PHONE: 301 496-7933

TERMS OF ACCEPTANCE: By acceptance of funds awarded under this grant, the grantee acknowledges that it will comply with terms and conditions in the following: (1) Legislation cited above; (2) Regulations cited above; (3) Provisions on or attached to this award notice and signed by the official(s) named below; (4) PHS Grants Administration Manual Chapters in effect on the beginning date of the grant Budget Period; (5) PHS Grants Policy Statement in effect on the beginning date of the grant Budget Period; (6) 45 CFR Part 74. The above order of precedence shall prevail.

FY - Common Accounting Number 2-8422644	CRS/Entity Identification No. 1620476816A1	PHS List No./Object Class Code /41.4E	Document Number (08)R6CA29490A
PROGRAM OFFICIAL FOR THIS GRANT  1079302  WILLIAM E. STRAILE, PH.D. DIVISION OF RESOURCES, CENTERS & COMMUNITY ACTIVITIES, NCI 301 427-8800		PHS Grants Management Official  <i>Leo F. Buscher, Jr</i> LEO F. BUSCHER, JR. GRANTS MANAGEMENT OFFICER NATIONAL CANCER INSTITUTE	

5 R26 CA 29490-02

TERMS OF AWARD

In compliance with the current Continuing Resolution, the total amount which was recommended for this budget period has been reduced by \$3,182 to a total approved direct cost budget of \$76,376.

1079303

Oak Ridge  
Associated  
Universities

Post Office Box 117  
Oak Ridge, Tennessee  
Telephone 615-576-1111

April 7, 1982

Dr. William R. Bibb, Director  
Research Division  
Department of Energy  
Oak Ridge, Tennessee 37830

Subject: RENEWAL APPLICATION FOR GRANT NO. CA 29490-02 WITH NIH,  
DOE NO. 20-81-80 ENTITLED "C-11-AMINO ACIDS/POSITRON ECT  
FOR PANCREATIC STUDIES"

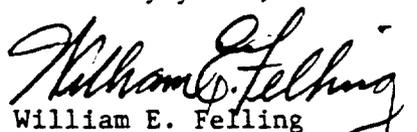
Dear Dr. Bibb:

Enclosed are three copies of an application to NIH for continuation of the subject grant. Draft copies of this proposal were forwarded to your office on March 25 for review, and approval for formal transmittal was given by Dr. Benson on April 5.

This project is under the direction of Dr. Karl Hübner and will be carried out under policies and procedures previously established between ORAU and DOE.

We will keep you advised of NIH action on this proposal.

Sincerely yours,

  
William E. Felling  
Acting Executive Director

RYAN:br

Enclosures

1079304

20-81-80

R 221

## SECTION I

Form Approved  
OMB No. 0925-0001

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE  <b>APPLICATION FOR CONTINUATION GRANT</b>	REVIEW GROUP	TYPE	ACTIVITY	GRANT NUMBER (Insert on all pages)
	SPC	5	F 26	CA 29490-02
	TOTAL PROJECT PERIOD			
From: 07/01/81		Through: 06/30/84		
REQUESTED BUDGET PERIOD				
From: 07/01/82		Through: 06/30/83		

To Be Verified By Applicant. Check Information in Items 1 Through 6. If Incorrect, Furnish Correct Information in Item 13.

1. TITLE			
C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES			
2A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Name and Address, Street, City, State, Zip Code)		4. APPLICANT ORGANIZATION (Name and Address, Street, City, State, Zip Code)	
HUBNER, KARL P OAK RIDGE ASSOCIATED UNIVERSIT P O BOX 117 OAK RIDGE, TENN 37830		OAK RIDGE ASSOCIATED UNIVERSITIES P O BOX 117 OAK RIDGE, TENN 37830	
2B. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT		5. ENTITY IDENTIFICATION NUMBER	
MEDICAL & HLTH SCIENCES DIV		1620476816A 1	
2C. MAJOR SUBDIVISION		6. TITLE AND ADDRESS OF OFFICIAL IN BUSINESS OFFICE OF APPLICANT ORGANIZATION	
MEDICAL & HEALTH SCIENCES DIV		HEAD, OFFICE OF FISCAL SERVICES OAK RIDGE ASSOCIATED UNIVERSITIES P O BOX 117 OAK RIDGE, TENN 37830	
3. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT (See Instructions)			
60 OTHER RESEAPCH ORGANIZATION			
COMPLETE THE FOLLOWING (See Instructions)			
7. HUMAN SUBJECTS, DERIVED MATERIAL OR DATA INVOLVED		11. INVENTIONS (See Instructions)	
<input type="checkbox"/> NO <input checked="" type="checkbox"/> YES (If "YES," form HHS 596 required)		<input checked="" type="checkbox"/> NO <input type="checkbox"/> Yes-not previously reported	
8. RECOMBINANT DNA RESEARCH SUBJECT TO NIH GUIDELINES		<input type="checkbox"/> Yes-previously reported	
<input checked="" type="checkbox"/> NO <input type="checkbox"/> YES		TELEPHONE INFORMATION	
9. PERFORMANCE SITE(S)		12A. PRINCIPAL INVESTIGATOR	
MEDICAL AND HEALTH SCIENCES DIVISION OAK RIDGE ASSOCIATED UNIVERSITIES P. O. BOX 117 OAK RIDGE, TENNESSEE 37830		OR PROGRAM DIRECTOR (Item 2a)	
		Area Code	
		615	
		Tele. No. & Ext.	
		576-3098	
		12B. NAME OF BUSINESS OFFICIAL (Item 6)	
		WILLIAM F. COUNTISS	
		615	
		576-3056	
		12C. NAME AND TITLE OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION (Item 15)	
		WILLIAM E. FELLING	
		615	
		576-3300	
10. DIRECT COSTS REQUESTED FOR BUDGET PERIOD			
\$99,558			
13. USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBER(S) WHERE ANSWER(S) APPLY.			
2B. NUCLEAR MEDICINE DEPARTMENT			

14. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSUR- ANCE: I Agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.	SIGNATURE OF PERSON NAMED IN 2A (In ink. "Per" signature not acceptable)	DATE
	<i>William F. Countiss</i>	4/8/82
15. CERTIFICATION AND ACCEPTANCE: I certify that the state- ments herein are true and complete to the best of my knowledge, and accept the obligation to comply with the Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense. (U.S. Code, Title 18, Section 1001.)	SIGNATURE OF PERSON NAMED IN 12C (In ink. "Per" signature not acceptable)	DATE
	<i>William E. Felling</i>	4/8/82

1079305

SECTION II

**SECTION II—BUDGET** (USUALLY 12 MONTHS)

FROM 07/01/82 THROUGH 06/30/83 GRANT NUMBER CA29490-02

A ITEMIZE DIRECT COSTS REQUESTED FOR NEXT BUDGET PERIOD DOLLAR AMOUNT REQUESTED (Omit cents)

PERSONNEL (Applicant organization only; See instructions)	TIME EFFORT		SALARY	FRINGE BENEFITS	TOTAL
	NAME	TITLE OF POSITION			
Hübner, Karl F.	Principal Investigator	20	8	10,584	2,597
Washburn, Lee C.	Scientist	10	4	3,787	867
Hayes, Raymond L.	Chief Scientist	5	2	NO CHARGE	
Gibbs, William D.	Scientist	20	10	6,636	1,540
Forester, Anita	Research Associate	100	40	14,555	2,682
SUBTOTALS				35,562	7,686

(Indicate cost of each item listed below)

TOTAL 43,248

CONSULTANT COSTS (See instructions) Paul King, Ph.D., Assoc. Professor, Bioengineering, Vanderbilt University; George Avant, Chief, Div. of Gastroenterology, Vanderbilt; R.I. Collmann, M.D., Gastroenterology, Knoxville, TN; A.P. Callahan, NMTG, Oak Ridge National Lab. 3,800

EQUIPMENT (Itemize)

0

SUPPLIES (Itemize by category)

Computer Discs 1,700  
 Photographic and Patient Supplies 1,200  
 Chemicals & Chromatographic Supplies 1,000  
 Glassware 500

4,400

TRAVEL DOMESTIC Consultant Travel (4 trips to Oak Ridge by King) 1,700  
 FOREIGN

PATIENT CARE COSTS INPATIENT  
 OUTPATIENT Patient Transportation & Lodging (30 trips) 1,500

ALTERATIONS AND RENOVATIONS (Itemize by category)

0

CONTRACTUAL OR THIRD PARTY COSTS (See instructions)

OTHER EXPENSES (Itemize by category)

Cyclotron time, 38 runs @ \$1,050 ea.: 39,900 (contains \$20,000 carryover from CA29490-01)

ECAT Maintenance & Repairs 4,510

Publication Costs 500

44,910

TOTAL DIRECT COST (Enter on Page 1 Item 10)

\$99,558\*

INDIRECT COST (See instructions)

60.5 % S&W\*  
 % TDC\*

\*If this is a special rate (e.g. off-site), explain

Date of DHMS Agreement

11/10/81 Provisional

Not Requested  
 Under negotiation with

1079306

## SECTION II—BUDGET (Continued)

Grant Number

CA 29490-02

B Supplemental information regarding ITEMS in the proposed budget for the next period which require explanation or justification (See instructions)

\*The proposed budget of \$99,558 for the period 07/01/82 - 06/30/83 includes a request to carryover \$20,000 from CA29490-01 to CA29490-02. We expect to underrun the current budget year by this amount because of the extended downtime at the Oak Ridge National Laboratory's 86" cyclotron. Extensive repair and modification of the cyclotron was begun on June 2, 1981. This work was delayed by an eight-week strike at Union Carbide, plus other mechanical problems which kept the cyclotron out of production until January 6, 1982. The cyclotron was operational at approximately 50% of its normal output capability between January 6 and February 12, 1982. During this time three cyclotron runs were made for this project, primarily for developmental work on the production of  $^{11}\text{C}$ -labeled L-valine,  $^{11}\text{C}$ -labeled L-tryptophan and clinical studies.

Included in the modification of the cyclotron was the installation of an automatic target changer which should result in more beam time for radionuclide production. With this capability, we are planning additional runs during the second year of this project in order to achieve our established goals. The \$20,000 carryover would be used for this purpose.

TRAVEL

We plan to use the \$1,700 requested for travel funds to enable Dr. Paul King to travel to Oak Ridge from Vanderbilt University, Nashville, TN four times during the year to spend five days each trip working on modifications to the ECAT scanner and consulting on this project. His cost per trip would be approximately as follows:

\$ 75.00	Transportation
200.00	Hotel
150.00	Per diem
<u>\$425.00</u>	TOTAL

CONSULTANT COSTS

Dr. Paul King's personal service agreement calls for \$150.00 fee per day. We are projecting 20 days of effort by Dr. King during the budget period. (\$3,000.)

The balance of the amount budgeted for consulting costs will be used for consultation with Dr. I. R. Collmann of the University of Tennessee Memorial Research Center and Hospital, Knoxville, Tennessee, and G. Avant, Vanderbilt University Hospital, Nashville, Tennessee on the clinical protocols to be followed and the interpretation of the clinical data. (\$800.00.)

1079307

## SECTION III

**SECTION III—DATA FOR  
CURRENT BUDGET PERIOD**  
(USUALLY 12 MONTHS)

FROM

07/01/81

THROUGH

06/30/82

GRANT NUMBER

CA29490-01

The following pertains to your CURRENT PHS budget. Do not include cost sharing funds. This information in conjunction with that provided on Page 2 will be used in determining the amount of support for the NEXT budget period.

A BUDGET	CURRENT BUDGET (As approved by awarding unit) (1)	ACTUAL EXPENDITURES THRU	ESTIMATED ADDITIONAL EXPENDITURES AND OBLIGATIONS FOR REMAINDER OF CURRENT BUDGET PERIOD (3)	TOTAL ESTIMATED EXPENDITURES AND OBLIGATIONS (Col 2 plus Col 3) (4)	ESTIMATED UNOBLIGATED BALANCE (Subtract Col 4 from Col 1) (5)
		02/28/82 (Insert Date) (2)			
TOTAL DIRECT COSTS	75,250	21,768	33,482	55,250	20,000 <sup>/2</sup>
INDIRECT COSTS (As Provided)	45,526 <sup>/1</sup>	13,170	20,257	33,426	
<b>TOTALS</b>	<b>\$120,776</b>	<b>\$ 34,938</b>	<b>\$ 53,739</b>	<b>\$ 88,676</b>	<b>\$</b>

**B THROUGH F**

See instructions and provide the information required in items B through F. Use this page and continuation pages as necessary.

**B. Professional Personnel**

Name	Title	Category	Less than 25%	26-50%	51-75%	More than 75%
Karl Hübner	Chief Clinician	2		*		
Lee Washburn	Scientist	2		*		
Raymond Hayes	Chief Scient.	2		X		
William D. Gibbs	Scientist	2		*		
Anita Forester	Research Assoc.	2				*

**C. Equipment.** None.**D. Travel.** None. See "E" below.

**E. Explanation of Column 5.** See complete explanation for cause of unexpended funds on Page 3. Because of the cyclotron downtime, no funds were used in the Travel, Consultants, or Patient Cost categories. In addition, cyclotron costs and supplies were also curtailed by this problem. These funds make up the \$20,000 underrun for this budget year.

**F. Other Support.**

Karl Hübner, M.D., Lee Washburn, Ph.D., and Raymond Hayes, Ph.D., and William Gibbs are supported in part under Department of Energy Contract DE-AC05-76OR00033, "Preclinical Development of Radiopharmaceuticals", \$438,000; "Clinical Development of Radiopharmaceuticals", \$222,000; "Radiation Emergency Assistance Center/Training Site (REAC/TS)", \$1,108.00.

<sup>/1</sup> As provided through the NIH Indirect Cost Management System.

<sup>/2</sup> Request for carryover of these funds is detailed on page 3.

## SECTION IV

APPLICANT REPEAT GRANT NUMBER SHOWN ON PAGE	GRANT NUMBER
<b>SECTION IV—SUMMARY PROGRESS REPORT</b>	CA 29490-01
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Last First Initial)	PERIOD COVERED BY THIS REPORT
Hübner, Karl F.	FROM THROUGH
NAME OF ORGANIZATION	
Oak Ridge Associated Universities	07/01/81 06/30/82
TITLE (Repeat title shown in item 1 on first page)	
C-11-Amino Acids/Positron ECT for Pancreatic Studies	

- 1 List all publications, not previously reported, resulting from work supported by this grant (author(s), title, page numbers, year, journal or book). List manuscripts separately as submitted for publication or accepted for publication.
- 2 Provide two reprints of publications not previously submitted to the awarding unit.
- 3 Progress Report. (See instructions)

1. The first two publications listed below resulted from work started between submission of the application of this grant and the start of the first funding period. This was also indicated in the second paragraph of the investigators' response to the critique in the resubmitted proposal in October, 1980.
  - 1.1 Resolution of C-11-DL-valine by high-performance liquid chromatography.  
L. C. Washburn, T. T. Sun, B. L. Byrd, and A. P. Callahan.  
J. Nucl. Med. 22:74, 1981. (abstract)
  - 1.2 Production of L-[1-<sup>11</sup>C]valine by HPLC Resolution.  
L. C. Washburn, T. T. Sun, B. L. Byrd, and A. P. Callahan.  
J. Nucl. Med. 23:29-33, 1982.
  - 1.3 Positron Emission Tomography (PET).  
K. F. Hubner and E. Buonocore.  
In Alimentary Tract Radiology, 3rd Edition, The C. V. Mosby Co., St. Louis, MO. (In press, 1982)
2. Two copies of two reprints and two preprints of the publications listed under 1 above are attached.
3. Progress has been made in three areas of the project.
  - 3.1 We have continued to investigate a high-performance liquid chromatographic (HPLC) method for resolution of <sup>11</sup>C-labeled amino acid racemates. This technique uses a commercial reverse-phase HPLC column and a chiral mobile phase containing L-proline and cupric acetate. Resolution of <sup>11</sup>C-DL-valine and <sup>11</sup>C-DL-tryptophan by HPLC has been scaled up to a preparative level. IND approvals for clinical studies of <sup>11</sup>C-L-valine and <sup>11</sup>C-L-tryptophan (copies of original IND and the amendment dated November 3, 1981 are attached) have been obtained from the FDA. <sup>11</sup>C-L-tryptophan has not yet been applied clinically, but it should be the agent of choice for pancreatic imaging, and in conjunction with <sup>11</sup>C-aminocyclopentanecarboxylic acid (<sup>11</sup>C-ACPC) or <sup>11</sup>C-aminocyclobutane carboxylic acid (<sup>11</sup>C-ACBC) may provide a means for the complete differential diagnosis of pancreatic carcinoma.
  - 3.2 Production of clinically useful quantities of <sup>11</sup>C-L-valine has been accomplished 12 times. A comparative study using <sup>11</sup>C-L-valine and <sup>11</sup>C-DL-valine in one patient with mild recurring pancreatitis during "remission" showed a significant difference between L-valine uptake (1.6681 µg/g) and DL-valine (0.635 µg/g,) a ratio of 2.6. This result was anticipated, at least as compared to data in mice, and reaffirms the need for <sup>11</sup>C-L-valine for physiological in vivo studies of pancreatic function, since the D- and L-forms are handled biochemically in entirely different ways.

## CONTINUATION SHEET

- 3.3 Essential to useful applications of positron tomography in clinical investigations are adequate computer programs for image data correction and quantitative image analysis. Progress in this area of this project consisted in rewriting and adapting the original ECAT programs and software to make them compatible with the ECAT-II system which was acquired and installed in December, 1981 (completion date). These programs are body outline calculation, a noise removal program, reading four images to common background, expansion of rectilinear scans, and listing of sort files. In addition, a program was developed to transfer patient data acquired on the original ECAT scanner.

Oak Ridge  
Associated  
Universities

Physics Division  
Oak Ridge National Laboratory  
P.O. Box 21708  
Oak Ridge, Tennessee 37831

March 25, 1982

Dr. William R. Bibb, Director  
Research Division  
Department of Energy  
Oak Ridge, Tennessee 37830

Subject: DRAFT APPLICATION FOR CONTINUATION SUPPORT OF A GRANT ENTITLED  
"C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES",  
NIH 5 R 26 CA29490-02, DOE NO. 20-81-80

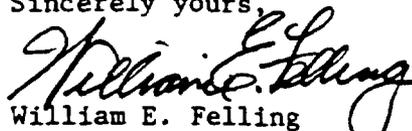
Dear Dr. Bibb:

Enclosed are three draft copies of a request for continuation of the subject grant. Dr. Karl Hübner is the principal investigator for this project, and this effort was most recently approved in your letter of July 22, 1981.

You will note on budget page 4 that we project a probable \$20,000 underrun for the current grant period. This underrun was caused by the prolonged downtime of the 86" cyclotron at ORNL for repair and modification. This work was delayed by the eight-week strike, and resulted in the cyclotron being unavailable for this project until January. It is still not operating at full capacity. Included in the modifications was the installation of an automatic target changer which should eventually provide more beam time for radionuclide production. We have discussed this situation with NIH and have been advised to request a carryover of \$20,000 into the second year of this grant. These funds would be used for additional cyclotron runs in the period 7/1/82 - 6/30/83.

NIH has requested that we submit this proposal earlier than the regular application date because special arrangements have been made for handling continuation grants for cancer research. We must forward the formal application to NIH prior to April 15. Should you have any questions during your review of this proposal, please call Dr. Hübner at 6-3098.

Sincerely yours,

  
William E. Felling  
Acting Executive Director

RYAN:br

Enclosures

1079311

20-81-80  
R 208

## SECTION I

Form Approved  
OMB No. 0925-00C

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE  <b>APPLICATION FOR CONTINUATION GRANT</b>	REVIEW GROUP	PE	ACTIVITY	GRANT NUMBER (Insert on all pages.)
	SRC	5	F 26	CA29490-02
	TOTAL PROJECT PERIOD			
From: 07/01/81		Through: 06/30/84		
REQUESTED BUDGET PERIOD				
From: 07/01/82		Through: 06/30/83		

To Be Verified By Applicant. Check Information In Items 1 Through 6. If Incorrect, Furnish Correct Information In Item 13.

## 1. TITLE

C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES

2A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR  
(Name and Address, Street, City, State, Zip Code)

HUBNER, KARL F  
OAK RIDGE ASSOCIATED UNIVERSIT  
P O BOX 117  
OAK RIDGE, TENN 37830

4. APPLICANT ORGANIZATION (Name and Address, Street, City, State,  
Zip Code)

OAK RIDGE ASSOCIATED  
UNIVERSITIES  
P O BOX 117  
OAK RIDGE, TENN 37830

## 5. ENTITY IDENTIFICATION NUMBER

1620476816A1

2B. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT  
MEDICAL & HLTH SCIENCES DIV

## 2C. MAJOR SUBDIVISION

MEDICAL &amp; HEALTH SCIENCES DIV

3. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR  
INSTITUTIONAL GRANT (See Instructions)

60 OTHER RESEAPCH ORGANIZATION

6. TITLE AND ADDRESS OF OFFICIAL IN BUSINESS OFFICE OF  
APPLICANT ORGANIZATION

HEAD, OFFICE OF FISCAL SERVICES  
OAK RIDGE ASSOCIATED  
UNIVERSITIES  
P O BOX 117  
OAK RIDGE, TENN 37830

COMPLETE THE FOLLOWING (See Instructions)

7. HUMAN SUBJECTS, DERIVED MATERIAL OR DATA INVOLVED  
 NO  YES (If "YES," form MHS 596 required)8. RECOMBINANT DNA RESEARCH SUBJECT TO NIH GUIDELINES  
 NO  YES

## 9. PERFORMANCE SITE(S)

MEDICAL AND HEALTH SCIENCES DIVISION  
OAK RIDGE ASSOCIATED UNIVERSITIES  
P. O. BOX 117  
OAK RIDGE, TENNESSEE 37830

## 11. INVENTIONS (See Instructions)

NO  Yes-not previously reported  
 Yes-previously reported

## TELEPHONE INFORMATION

12A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Item 2a)	Area Code	Tele. No. & Ext.
	615	576-3098
12B. NAME OF BUSINESS OFFICIAL (Item 6)		
WILLIAM F. COUNTISS	615	576-3056
12C. NAME AND TITLE OF OFFICIAL SIGNING FOR APPLICANT ORGANIZATION (Item 15)		
WILLIAM E. FELLING ACTING EXECUTIVE DIRECTOR	615	576-3300

## 10. DIRECT COSTS REQUESTED FOR BUDGET PERIOD

13. USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBER(S) WHERE ANSWER(S) APPLY.

2B. NUCLEAR MEDICINE DEPARTMENT

14. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.	SIGNATURE OF PERSON NAMED IN 2A (In ink. "Per" signature not acceptable)	DATE
15. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with the Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense. (U.S. Code, Title 18, Section 1001.)	SIGNATURE OF PERSON NAMED IN 12C (In ink. "Per" signature not acceptable)	DATE

1079312



## SECTION I BUDGET (Continued)

CA29490-02

E. Supplemental information regarding ITEMS in the proposed budget for the next period which require explanation or justification. (See instructions)

\*The proposed budget for the period 07/01/82 - 06/30/83 includes a request to carryover \$20,000 from CA29490-01 to CA29490-02. We expect to underrun the current budget year by this amount because of extended downtime at the Oak Ridge National Laboratory's 86" cyclotron. Extensive repair and modification of the cyclotron was begun on June 2, 1981. This work was delayed by an eight-week strike at Union Carbide, plus other mechanical problems which kept the cyclotron out of production until January 6, 1982. The cyclotron was operational at approximately 50% of its normal output capability between January 6 and February 12, 1982. During this time three cyclotron runs were made for this project, primarily for developmental work on the production of  $^{11}\text{C}$ -labeled L-valine,  $^{11}\text{C}$ -labeled L-tryptophan and clinical studies.

Included in the modification of the cyclotron was the installation of an automatic target changer which should result in more beam time for radionuclide production. With this capability, we are planning additional runs during the second year of this project in order to achieve our established goals. The \$20,000 carryover would be used for this purpose.

1079314

SECTION III—DATA FOR  
CURRENT BUDGET PERIOD

FROM

07/01/81

THROUGH

06/30/82

GRANT NUMBER

CA29490

The following pertains to your CURRENT PHS budget. Do not include cost sharing funds. This information in conjunction with that provided on Page 2 will be used in determining the amount of support for the NEXT budget period.

A. BUDGET	CURRENT BUDGET (As approved by awarding unit.) (1)	ACTUAL EXPENDITURES THROUGH	ESTIMATED ADDITIONAL EXPENDITURES AND OBLIGATIONS FOR REMAINDER OF CURRENT BUDGET PERIOD (3)	TOTAL ESTIMATED EXPENDITURES AND OBLIGATIONS (Col. 2 plus Col. 3) (4)	ESTIMATED UNOBLIGATED BALANCE (Subtract Col. 4 from Col. 2) (5)
		02-28-82 (Insert Date) (2)			
TOTAL DIRECT COSTS	75,250	21,768	33,482	55,250	20,000**
INDIRECT COSTS (As Provided)	45,526*	13,170	20,257	33,426	
TOTALS	\$ 120,776	\$ 34,938	\$ 53,739	\$ 88,676	\$

## E THROUGH F

See instructions and provide the information required in items E through F. Use this page and continuation pages as necessary.

NOTE: Detailed information on personnel costs and travel expenses will be included in final submission.

REMOVE AND USE FOR DRAFT COPY

S1E6L01  
1079315

\* As provided through the NIH Indirect Cost Management System.

\*\* Request for carryover of these funds is detailed on page 3.

## SECTION IV—SUMMARY PROGRESS REPORT

CA 29490

PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Last, First, Initial)

Hübner, Karl F.

PERIOD COVERED BY THIS REPORT

FROM

THROUGH

NAME OF ORGANIZATION

Oak Ridge Associated Universities

07/01/81

06/30/82

LE: Repeat title shown in item 1 on first page.

C-11-Amino Acids/Positron ECT for Pancreatic Studies

1. List all publications not previously reported resulting from work supported by this grant (author(s), title, page numbers, year, journal or book). List manuscripts separately, as submitted for publication or accepted for publication.
2. Provide two reprints of publications not previously submitted to the awarding unit.
3. Progress Report. (See instructions)

1. The first two publications listed below resulted from work started between submission of the application of this grant and the start of the first funding period. This was also indicated in the second paragraph of the investigators' response to the critique in the resubmitted proposal in October, 1980.

1.1 Resolution of C-11-DL-valine by high-performance liquid chromatography.  
L. C. Washburn, T. T. Sun, B. L. Byrd, and A. P. Callahan.  
J. Nucl. Med. 22:74, 1981. (abstract)

1.2 Production of L-[1-<sup>11</sup>C]valine by HPLC Resolution.  
L. C. Washburn, T. T. Sun, B. L. Byrd, and A. P. Callahan.  
J. Nucl. Med. 23:29-33, 1982.

1.3 Positron Emission Tomography (PET).  
K. F. Hübner and E. Buonocore.  
In Alimentary Tract Radiology, 3rd Edition, The C. V. Mosby Co.,  
St. Louis, MO. (In press, 1982)

2. Two copies of two reprints and two preprints of the publications listed under 1 above are attached.

3. Progress has been made in three areas of the project.

3.1 We have continued to investigate a high-performance liquid chromatographic (HPLC) method for resolution of <sup>11</sup>C-labeled amino acid racemates. This technique uses a commercial reverse-phase HPLC column and a chiral mobile phase containing L-proline and cupric acetate. Resolution of <sup>11</sup>C-DL-valine and <sup>11</sup>C-DL-tryptophan by HPLC has been scaled up to a preparative level. IND approvals for clinical studies of <sup>11</sup>C-L-valine and <sup>11</sup>C-L-tryptophan (copies of original IND and the amendment dated November 3, 1981 are attached) have been obtained from the FDA. <sup>11</sup>C-L-tryptophan has not yet been applied clinically, but it should be the agent of choice for pancreatic imaging, and in conjunction with <sup>11</sup>C-aminocyclopentanecarboxylic acid (<sup>11</sup>C-ACPC) or <sup>11</sup>C-aminocyclobutane carboxylic acid (<sup>11</sup>C-ACBC) may provide a means for the complete differential diagnosis of pancreatic carcinoma.

3.2 Production of clinically useful quantities of <sup>11</sup>C-L-valine has been accomplished 12 times. A comparative study using <sup>11</sup>C-L-valine and <sup>11</sup>C-DL-valine in one patient with mild recurring pancreatitis during "remission" showed a significant difference between L-valine uptake (1.6681 µg/g) and DL-valine (0.635 µg/g, a ratio of 2.6. This result was anticipated, at least as compared to data in mice, and reaffirms the need for <sup>11</sup>C-L-valine for physiological in vivo studies of pancreatic function, since the D- and L-forms are handled biochemically in entirely different ways.

CONTINUATION SHEET

- 3.3 Essential to useful applications of positron tomography in clinical investigations are adequate computer programs for image data correction and quantitative image analysis. Progress in this area of this project consisted in rewriting and adapting the original ECAT programs and software to make them compatible with the ECAT-II system which was acquired and installed in December, 1981 (completion date). These programs are body outline calculation, a noise removal program, reading four images to common background, expansion of rectilinear scans, and listing of sort files. In addition, a program was developed to transfer patient data acquired on the original ECAT scanner.

Oak Ridge  
Associated  
Universities

1000 Oak Ridge  
Oak Ridge, Tennessee  
Telephone 615-576-1000

October 24, 1980

Dr. William R. Bibb, Director  
Research Division  
Department of Energy  
Oak Ridge, Tennessee 37830

Subject: REVISED GRANT APPLICATION (NIH CA29490-01) ENTITLED *C-11-AMINO  
ACIDS/POSITRON ECT FOR PANCREATIC STUDIES*

Dear Dr. Bibb:

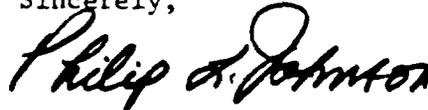
Enclosed are three copies of a revised grant application to NIH for support of a project entitled *C-11-Amino Acids/Positron ECT for Pancreatic Studies*. This proposal was originally submitted in March of this year and was assigned the number CA29490-01 by NIH. It was reviewed and approved, but not funded. The enclosed application incorporates changes in text recommended by the review panel. These changes are set off from the original text per instructions from NIH.

Since this proposal was approved by DOE for submission in March, we are simultaneously transmitting this revised version to NIH and DOE. Should your office have any objections to the proposal, it can be withdrawn before the review panel meets.

The proposed research will be carried out under policies and procedures previously established between ORAU and DOE and will be supervised by Dr. Karl F. Hübner.

We will keep you advised concerning the status of this grant.

Sincerely,



Philip L. Johnson  
Executive Director

RYAN:br

Enclosures

1079318

20-81-80

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE PUBLIC HEALTH SERVICE  <b>GRANT APPLICATION</b>  FOLLOW INSTRUCTIONS CAREFULLY	LEAVE BLANK <table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:33%;">TYPE</td> <td style="width:33%;">ACTIVITY</td> <td style="width:33%;">NUMBER</td> </tr> <tr> <td colspan="2">REVIEW GROUP</td> <td>FORMERLY</td> </tr> <tr> <td colspan="2">COUNCIL BOARD (Month, year)</td> <td>DATE RECEIVED</td> </tr> </table>	TYPE	ACTIVITY	NUMBER	REVIEW GROUP		FORMERLY	COUNCIL BOARD (Month, year)		DATE RECEIVED
TYPE	ACTIVITY	NUMBER								
REVIEW GROUP		FORMERLY								
COUNCIL BOARD (Month, year)		DATE RECEIVED								

1. TITLE OF APPLICATION (Do not exceed 56 typewriter spaces)  
**C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES**

2. RESPONSE TO SPECIFIC PROGRAM ANNOUNCEMENT  NO  YES (If "YES," state RFA number and/or announcement title)

**3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR**

3a. NAME (Last, first, middle) **Hübner, Karl F.**      3b. SOCIAL SECURITY NUMBER XXXXXXXXXX

3c. MAILING ADDRESS (Street, city, state, zip code)  
**Oak Ridge Associated Universities  
 P. O. Box 117  
 Oak Ridge, TN. 37830**

3d. POSITION TITLE  
**Chief Clinician, Medical and Health Sciences Division**

3e. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT  
**Medical and Health Sciences Division**

3f. TELEPHONE (Area code, number and extension)  
**615-576-3098**

3g. MAJOR SUBDIVISION  
**Medical and Health Sciences Division**

4. HUMAN SUBJECTS, DERIVED MATERIALS OR DATA INVOLVED  
 NO  YES (If "YES," form HEW 596 required)

5. RECOMBINANT DNA RESEARCH SUBJECT TO NIH GUIDELINES  
 NO  YES

6. DATES OF ENTIRE PROPOSED PROJECT PERIOD (This application)  
 From: **7/1/81** Through: **6/30/84**

7. TOTAL DIRECT COSTS REQUESTED FOR PROJECT PERIOD (from page 5)  
**\$ 243,400**

8. DIRECT COSTS REQUESTED FOR FIRST 12-MONTH BUDGET PERIOD (from page 4)  
**\$ 75,750**

9. PERFORMANCE SITES (Organizations and addresses)  
**Medical and Health Sciences Division  
 Oak Ridge Associated Universities  
 P. O. Box 117  
 Oak Ridge, Tennessee 37830**

10. INVENTIONS (Competing continuation application only)  
 Were any inventions conceived or reduced to practice during the course of the project?  
 NO  YES - Previously reported  
 YES - Not previously reported

11. APPLICANT ORGANIZATION (Name, address, and congressional district)  
**Oak Ridge Associated Universities  
 P. O. Box 117  
 Oak Ridge, Tennessee 37830  
 Congressional District No. 3**

12. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT (See instructions)

13. ENTITY IDENTIFICATION NUMBER  
**1620476816A**

Code  Description:

14. TYPE OF ORGANIZATION (See instructions)  
 Private Nonprofit  
 Public (Specify Federal, State, Local):

15. OFFICIAL IN BUSINESS OFFICE TO BE NOTIFIED IF AN AWARD IS MADE (Name, title, address and telephone number.)  
**W. F. Countiss  
 Head, Office of Fiscal Services  
 Oak Ridge Associated Universities  
 P. O. Box 117  
 Oak Ridge, TN. 37830 615-576-3056**

16. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION (Name, title, address and telephone number)  
**Dr. Philip L. Johnson  
 Executive Director  
 Oak Ridge Associated Universities  
 P. O. Box 117  
 Oak Ridge, TN. Ph. 615-576-3300**

17. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PERSON NAMED IN 3a (In ink. "Per" signature not acceptable)  
**Karl F. Hübner, M.D.**      10/22/80

18. CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true and complete to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense. (U.S. Code, Title 18, Section 1001.)

SIGNATURE OF PERSON NAMED IN 16 (In ink. "Per" signature not acceptable)      DATE  
**Philip L. Johnson**      10/27/80

1079319

ABSTRACT OF RESEARCH PLAN

NAME AND ADDRESS OF APPLICANT ORGANIZATION (Same as Item 11, page 1)

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

TITLE OF APPLICATION (Same as Item 1, page 1)

C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES

Name, Title and Department of all professional personnel engaged on project, beginning with Principal Investigator/Program Director

Karl F. Hübner	Chief Clinician, Medical and Health Sciences Division (M&HSD)
Lee C. Washburn	Scientist, M&HSD
Raymond L. Hayes	Chief Scientist, M&HSD
Paul H. King	Associate Professor, Dept. of Biomedical Engineering, Vanderbilt University, Nashville, Tennessee

ABSTRACT OF RESEARCH PLAN: Concisely describe the application's specific aims, methodology and long-term objectives, making reference to the scientific disciplines involved and the health-relatedness of the project. The abstract should be self-contained so that it can serve as a succinct and accurate description of the application when separated from it. DO NOT EXCEED THE SPACE PROVIDED.

Cancer of the pancreas is one of the leading causes of death among cancer patients. This can be attributed in part to the fact that a definitive diagnosis is usually made only at an advanced stage of the disease. We have shown, using positron emission computerized tomography (positron ECT) that  $^{11}\text{C}$ -labeled DL-tryptophan and DL-valine have high preferential uptakes in normal pancreatic tissue. Since the L-isomers of these two amino acids have an affinity for normal pancreas while the D-isomers tend to be preferentially taken up by tumor tissue, approximately the same  $^{11}\text{C}$  concentrations occur in both normal and malignant pancreatic tissues with the DL mixture. We propose to use  $^{11}\text{C}$ -labeled L-tryptophan or L-valine to detect pancreatic cancer as zones of decreased or absent  $^{11}\text{C}$  concentrations in the pancreas in the three-dimensional cross-sectional images obtained with positron ECT. Confirmation of the presence of a malignant lesion(s) would then be made with  $^{11}\text{C}$ -labeled l-aminocyclopentanecarboxylic acid or its cyclobutane analog, radiopharmaceuticals which we have shown to have no affinity for inflammatory lesions and to be effective tumor-localizing agents. This diagnostic protocol should thus provide a non-invasive method for the differential diagnosis of pancreatic disease. The studies will be done with an up-to-date emission computerized tomograph, an EG&G ORTEC ECAT-II (TM). We also propose to use positron ECT to quantitatively measure the effect of therapy on the extraction/utilization of amino acids by pancreatic neoplasms as a possible method of metabolically gauging individual responses to treatment.

LABORATORY ANIMALS INVOLVED. Identify by common names. If none, state "none"  
None.

## TABLE OF CONTENTS

Number pages consecutively at the bottom throughout the application. Do not use suffixes such as 5a, 5b. Type the name of the Principal Investigator/Program Director at the top of each printed page and each continuation page.

SECTION 1.	<u>PAGE NUMBERS</u>
Face Page, Abstract, Table of Contents.....	1-3
Detailed Budget for First 12 Month Budget Period .....	4
Budget Estimates for All Years of Support.....	5
Biographical Sketch-Principal Investigator/Program Director (Not to exceed two pages).....	<u>6-7</u>
Other Biographical Sketches (Not to exceed two pages for each).....	<u>8-14</u>
Other Support.....	<u>15-16</u>
Resources and Environment .....	<u>17</u>
SECTION 2.	
Introduction (Excess pages; revised and supplemental applications) .....	<u>18-19</u>
Research Plan	
A. Specific Aims (Not to exceed one page) .....	<u>20</u>
B. Significance (Not to exceed three pages).....	<u>20-23</u>
C. Progress Report/Preliminary Studies (Not to exceed eight pages) .....	<u>23-25</u>
D. Methods .....	<u>25-31</u>
E. Human Subjects, Derived Materials or Data.....	<u>31-32</u>
F. Laboratory Animals .....	<u>32</u>
G. Consultants.....	<u>32</u>
H. Consortium Arrangements or Formalized Collaborative Agreements .....	<u>32-33</u>
I. Literature Cited .....	<u>34-35</u>
Checklist .....	<u>36</u>

SECTION 3. Appendix (Six sets) (No page numbering necessary for Appendix)

Number of publications: 1 (Appendix A) Number of manuscripts: \_\_\_\_\_  
 Other items (list):

- B. Examples of positron tomographic scans obtained with <sup>11</sup>C-labeled amino acids.
- C. Example of analytical-scale resolution of <sup>11</sup>C-DL-tryptophan using high pressure liquid chromatography.

Application Receipt Record, form PHS 3830  
 Form HEW 596 if Item 4, page 1, is checked "YES"



**BUDGET ESTIMATES FOR ALL YEARS OF SUPPORT REQUESTED  
DIRECT COSTS ONLY**

BUDGET CATEGORY TOTALS		1st BUDGET PERIOD (from page 4)	ADDITIONAL YEARS SUPPORT REQUESTED			
			2nd	3rd	4th	5th
PERSONNEL (Salary and fringe benefits.) (Applicant organization only)		40,800	44,050	47,600		
CONSULTANT COSTS		3,600	3,800	4,000		
EQUIPMENT		0	0	0		
SUPPLIES		4,150	4,400	4,650		
TRAVEL	DOMESTIC	1,700	1,800	1,900		
	FOREIGN					
PATIENT CARE COSTS	INPATIENT					
	OUTPATIENT	1,500	1,500	1,500		
ALTERATIONS AND RENOVATIONS						
CONTRACTUAL OR THIRD PARTY COSTS						
OTHER EXPENSES		24,000	25,450	27,000		
TOTAL DIRECT COSTS		75,750	81,000	86,650		
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Also enter on page 1, item 7) →					\$ 243,400	

JUSTIFICATION (Use continuation pages if necessary): Briefly describe the specific functions of the personnel and consultants. For all years, justify any costs for which the need may not be obvious, such as equipment, foreign travel, alterations and renovations, and contractual or third party costs. For future years, justify any significant increases in any category. In addition, for **COMPETING CONTINUATION** applications, justify any significant increases over current level of support. If a recurring annual increase in personnel costs is anticipated, give percentage.

Recurring increases in personnel costs computed at 8% average.

Personnel Functions:

Hübner, Karl F.-(Principal Investigator) oversees conduct of project.

Washburn, Lee C.-Oversees production of radiopharmaceuticals.

Hayes, Raymond L.-Provides advise in radiopharmaceutical development.

Gibbs, Wm. D.-Physicist and Nuclear Medical Technologist in clinical positron emission computerized tomography.

Sun, Tan Tan-Chemist involved in production of radiopharmaceuticals.

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME Karl F. Hübner, M.D.	TITLE Chief Clinician Medical & Health Sciences Div.	BIRTHDATE Mo., Day, Year [REDACTED]
------------------------------	--	--

EDUCATION (Begin with baccalaureate training and include postdoctoral)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- 1962-1964 Resident in Clinical Investigation, Medical Division, Oak Ridge Institute of Nuclear Studies (now Oak Ridge Associated Universities), Oak Ridge, TN.
- 1964-1967 Resident in Pediatrics, University of Tübingen, Medical School, Germany.
- 1967-1970 Research Associate in Experimental Immunology, Medical Division, Oak Ridge Associated Universities, Oak Ridge, TN.
- 1971-1973 Senior Staff Member with Clinical Staff, Medical Division, Oak Ridge Associated Universities, Oak Ridge, TN.
- 1973-1979 Senior Research Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.
- 1975-1979 Director, Outpatient Nuclear Medicine, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.
- 1977-Present Director, Radiation Emergency Assistance Center/Training Site, Oak Ridge Associated Universities, Oak Ridge, TN.
- 1979-Present Chief Clinician, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.

Honors: 1954 "Scheffel Preis" for History and German.  
[REDACTED]  
1979 American Men and Women in Science; listed in Guide to Energy Specialists, International Environment Information.

Publications:

Swartzendruber, D.C. and Hübner, K.F. Effect of external whole-body X-irradiation on gallium-67 retention in mouse tissues. Radiat. Res. 55:457-468, 1973.

Hübner, K.F., Andrews, G.A., Hayes, R.L., Poggenburg, J.K., and Solomon, A. The use of rare earth radionuclides and other bone-seekers in evaluating bone lesions in patients with multiple myeloma and solitary plasmacytoma. Radiology 125:171-176, October, 1977.

Hübner, K.F., Andrews, G.A., Washburn, L., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Winebrenner, J.D. Tumor location with 1-aminocyclopentane[<sup>11</sup>C]-carboxylic acid: preliminary clinical trials with single-photon detection. J. Nucl. Med. 18:1215-1221, 1977.

Johnston, G.S., Go, M.F., Benua, R.S., Larson, S.M., Andrews, G.A., and Hübner, K.F. <sup>67</sup>Ga-citrate imaging in Hodgkin's disease: final report of cooperative group. J. Nucl. Med. 18:692-698, 1977.

NAME (last, first, middle initial)

Hübner, Karl F.

SOCIAL SECURITY NUMBER

Continuation page

Andrews, G.A., Hübner, K.F., and Greenlaw, R.H. Gallium-67 citrate imaging in malignant lymphoma: final report of cooperative group. J. Nucl. Med. 19:1013-19, 1978.

Hübner, K.F., Andrews, G.A., Gibbs, W.D., Holloway, S., Hayes, R.L., and Washburn, L.C. Initial diagnostic results with <sup>11</sup>C-labeled amino acids and the emission positron tomograph. In Proceedings of the Second World Federation of Nuclear Medicine and Biology, p. 13\*(abstract), Washington, D.C., 1978.

Lawless, D., Brown, D.H., Hübner, K.F., Colyer, S.P., Carlton, J.E., and Hayes, R.L. Isolation and partial characterization of a <sup>67</sup>Ga-binding glycoprotein from Morris 5123C rat hepatoma. Can. Res. 38:4440-4444, 1978.

Sauerbrunn, B.J.L., Andrews, G.A., and Hübner, K.F. <sup>67</sup>Ga-citrate imaging in genitourinary tract tumors: report of cooperative study. J. Nucl. Med. 19:470-475, 1978.

Buonocore, E., and Hübner, K.F. Positron-emission computed tomography of the pancreas: a preliminary study. Radiology 133:195-201, 1979.

Buonocore, E., Hübner, K.F., and Collmann, I.R. Differentiation of retroperitoneal tumor using positron emission computed tomography. J. Comput. Asst. Tomogr. 3(6):825-828, 1979.

Hübner, K.F., Andrews, G.A., Buonocore, E., Hayes, R.L., Washburn, L.C., Collmann, I.R., and Gibbs, W.D. Carbon-11-labeled amino acids for the rectilinear and positron tomographic imaging of the human pancreas. J. Nucl. Med. 20:507-513, 1979.

Hübner, K.F., and Buonocore, E. Emission computerized tomography (ECT) with <sup>11</sup>C-labeled amino acids, transmission CT and ultrasonography (US) in the diagnosis of pancreatic disease. Presented at the Sixth International Congress of Radiation Research, Tokyo, Japan, 1979 (abstract).

Hübner, K.F., Andrews, G.A., Washburn, L., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Winebrenner, J.D. Tumor location with l-aminocyclopentane[<sup>11</sup>C]-carboxylic acid: preliminary clinical trials with single-photon detection. In Year Book of Cancer, R.L. Clark, R.W. Cumley and R.C. Hickey, eds., Year Book Medical Publishers, Inc., Chicago, 1979, pp. 237-239.

Hübner, K.F., Buonocore, E., Gibbs, W.D., Holloway, S., and Byrd, B.L. Differentiation of pancreatic and other retroperitoneal tumors by positron emission computerized tomography (ECT). J. Nucl. Med. 20:631, 1979.

King, P., Hübner, K.F., Gibbs, W.D., and Holloway, E. Noise identification and removal in positron imaging systems. In Proceedings of IEEE-Transactions on Nuclear Science, February, 1981. (in press)

Hübner, K.F., King, P., Gibbs, W.D., Washburn, L.C., and Hayes, R.L. Positron emission computerized tomography: A potential tool for in vivo quantitation of the distribution of radiopharmaceuticals. In Proceedings of the Third International Radiopharmaceutical Dosimetry Symposium, Oak Ridge, TN, October 7-10, 1980. (in press)

DO NOT TYPE IN THIS SPACE-BINDING MARGIN

1079325

page 7

BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)		
Lee C. Washburn	Scientist	[REDACTED]		
EDUCATION (Begin with baccalaureate training and include postdoctoral)				
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY	
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages:

March-June 1972                      Research Associate, Vanderbilt University, Nashville, TN.  
 June 1972-March 1974              Presidential Intern, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.  
 April 1974-present                 Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.

Honors:                                Alpha Chi; Shell Oil Foundation Predoctoral Fellowship 1971-1972.

Publications:

Washburn, L.C., Coffey, J.L., Watson, E.E., Sun, T.T., and Hayes, R.L. Radiation dosimetry of some <sup>11</sup>C-labeled amino acid pharmaceuticals. In Radiopharmaceutical Dosimetry Symposium, R.J. Cloutier, J.L. Coffey, W.S. Snyder, and E.E. Watson, eds., U. S. Dept. of Health, Education and Welfare, Washington, D.C., June 1976, pp. 441-451.

Hayes, R.L., Washburn, L.C., Wieland, B.W., Sun, T.T., Turtle, R.R., and Butler, T.A. Carboxyl-labeled <sup>11</sup>C-l-aminocyclopentanecarboxylic acid, a potential agent for cancer detection. J. Nucl. Med. 17:748-751, 1976.

Hübner, K.F., Andrews, G.A., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Winebrenner, J.D. Tumor location with l-aminocyclopentane [<sup>11</sup>C] carboxylic acid: preliminary clinical trials with single-photon detection. J. Nucl. Med. 18:1215-1221, 1977.

Hayes, R.L., Washburn, L.C., Wieland, B.W., Sun, T.T., Butler, T.A., and Callahan, A.P. Synthesis and purification of <sup>11</sup>C-carboxyl-labeled amino acids. J. Appl. Radiat. Isotopes 29:186-187, 1978.

Washburn, L.C., Wieland, B.W., Sun, T.T., Hayes, R.L., and Butler, T.A. [1-<sup>11</sup>C] DL-valine, a potential pancreas-imaging agent. J. Nucl. Med. 19:77-83, 1978.

Washburn, L.C., Sun, T.T., Anon, J.B., and Hayes, R.L. Effect of structure on tumor specificity of alicyclic α-amino acids. Cancer Res. 38:2271-2273, 1978.

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., Butler, T.A., and Callahan, A.P. High-level production of C-11-carboxyl-labeled amino acids. In Radiopharmaceuticals II, proceedings of 2nd International Symposium on Radiopharmaceuticals, Seattle, Wash., 1979, pp. 767-777.

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. DL-[Carboxyl-<sup>11</sup>C] tryptophan, a potential agent for pancreatic imaging: production and pre-clinical investigations. J. Nucl. Med. 20:857-864, 1979.

Continuation page

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. [Carboxyl- $^{11}\text{C}$ ] 1-aminocyclobutanecarboxylic acid, a potential agent for tumor localization. J. Nucl. Med. 20:1055-1061, 1979.

Hübner, K.F., Andrews, G.A., Buonocore, E., Hayes, R.L., Washburn, L.C., Collmann, I.R., and Gibbs, W.D. Carbon-11-labeled amino acids for the rectilinear and positron tomographic imaging of the human pancreas. J. Nucl. Med. 20:507-513, 1979.

Digenis, G.A., Casey, D.L., Wesner, D.A., Washburn, L.C., and Hayes, R.L. Preparation of optically active C-11-amino acids. J. Nucl. Med. 20:662, 1979 (abstract).

Blank, M.L., Cress, E.A., Byrd, B.L., Washburn, L.C., and Snyder, F. Liposomal encapsulated Zn-DTPA for removing intracellular heavy metals. Health Phys. (in press)

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Washburn, L.C., Ringenberg, R.E., Sun, T.T., and Hayes, R.L.  $^{11}\text{C}$ -labeled 1-aminocyclohexanecarboxylic acid ( $^{11}\text{C}$ -ACHC), a potential agent for studies of amino acid transport in the brain. Proceedings of the Third International Symposium on Radiopharmaceutical Chemistry, St. Louis, Missouri, June, 1980. (To be published in J. Labelled Compounds and Radiopharmaceuticals.)

Jay, M., Digenis, G.A., Chaney, J.E., Washburn, L.C., Byrd, B.L., Hayes, R.L., and Callahan, A.P. Synthesis and brain uptake of carbon-11 phenethylamine. Proceedings of the Third International Symposium on Radiopharmaceutical Chemistry, St. Louis, Missouri, June, 1980. (To be published in J. Labelled Compounds and Radiopharmaceuticals.)

Kabalka, G.S., Gooch, E.E., Sun, T.T., and Washburn, L.C. A rapid and mild method for labeling functionally substituted molecules with iodine radionuclides. Proceedings of the Third International Symposium on Radiopharmaceutical Chemistry, St. Louis, Missouri, June, 1980. (To be published in J. Labelled Compounds and Radiopharmaceuticals.)

Casey, D.L., Digenis, G.A., Wesner, D.A., Washburn, L.C., Chaney, J.E., Hayes, R.L., and Callahan, A.P. Preparation and preliminary tissue studies of optically active C-11-D- and L-phenylalanine. (Submitted to Int. J. Appl. Radiat. Isot.)

Hübner, K.F., Washburn, L.C., Gibbs, W.D., Hayes, R.L., and Holloway, E.C. Tumor detection with 1-aminocyclopentane and 1-aminocyclobutane [ $^{11}\text{C}$ ]carboxylic acid using positron emission computerized tomography. (Submitted to J. Nucl. Med.)

Hübner, K.F., King, P., Gibbs, W.D., Partain, C.L., Washburn, L.C., Hayes, R.L., and Holloway, E. Clinical investigations with  $^{11}\text{C}$ -labeled amino acids using positron emission computerized tomography in patients with neoplastic diseases. In Proceedings of the IAEA International Symposium on Radionuclide Imaging, Heidelberg, Germany, 1980. (In press.)

Washburn, L.C., Dees, L., Byrd, B.L., Sun, T.T., and Hayes, R.L.  $^{11}\text{C}$ -labeled  $\alpha$ -aminoisobutyric acid, a potential agent for positron tomographic assessment of blood-brain barrier disruption. In Proceedings of the 21st Annual Meeting, Southeastern Chapter, Society of Nuclear Medicine (Continuing Education Lectures), Nashville, TN. (Abstract)

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**BIOGRAPHICAL SKETCH**

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTHDATE (Mo., Day, Yr.)	
Raymond L. Hayes	Chief Scientist	[REDACTED]	
EDUCATION (Begin with baccalaureate training and include postdoctoral)			
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

**RESEARCH AND/OR PROFESSIONAL EXPERIENCE:** Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

1944 Senior Chemist, U.S. Rubber Co., Charlotte, NC  
 1950-present Chief Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN  
 Honors: Sigma Xi; AEC (NSF) Predoctoral Fellowship 1948-1950

Wieland, B.W., Washburn, L.C., Turtle, R.R., Hayes, R.L., and Butler, T.A. Development of cyclotron targetry and remote radiochemical techniques for the continuous large-scale production of <sup>11</sup>C-labeled amino acids. J. Labeled Compds. Radiopharmaceuticals 13(2):202, 1977.

Washburn, L.C., Wieland, B.W., Sun, T.T., and Hayes, R.L. <sup>11</sup>C-labeled amino acids as agents for tumor and pancreas visualization. J. Labeled Compds. Radiopharmaceuticals 13:203, 1977.

Hübner, K.F., Andrews, G.A., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Winebrenner, J.D. Tumor location with 1-aminocyclopentane [<sup>11</sup>C] carboxylic acid: preliminary clinical trials with single-photon detection. J. Nucl. Med. 18:1215-1221, 1977.

Hübner, K.F., Andrews, G.A., Hayes, R.L., Poggenburg, J.K., Jr., and Solomon, A. The use of rare-earth radionuclides and other bone-seekers in the evaluation of bone lesions in patients with multiple myeloma or solitary plasmacytoma. Radiology 125(1):171-176, 1977.

Hayes, R.L. The tissue distribution of gallium radionuclides. J. Nucl. Med. 18:740-742, 1977.

Washburn, L.C., Wieland, B.W., Sun, T.T., Hayes, R.L., and Butler, T.A. [1-<sup>11</sup>C] DL-valine, a potential pancreas-imaging agent. J. Nucl. Med. 19:77-83, 1978.

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Hayes, R.L., Washburn, L.C., Wieland, B.W., Sun, T.T., Turtle, R.R., and Butler, T.A. Carboxyl-labeled <sup>11</sup>C-1-aminocyclopentanecarboxylic acid, a potential agent for cancer detection. Year Book of Cancer 1978, pp. 236-237.

Washburn, L.C., Sun, T.T., Anon, J.B., and Hayes, R.L. Effect of structure on tumor specificity of alicyclic α-amino acids. Cancer Res. 38:2271-2273, 1978.

Hayes, R.L. The medical use of gallium radionuclides: a brief history with some comments. Semin. Nucl. Med. 8:183-191, 1978.

NAME (last, first, middle initial)

Hubner, Karl F.

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Lawless, D., Brown, D.H., Hubner, K.F., Colyer, S.P., Carlton, J.E., and Hayes, R.L. Isolation and partial characterization of a  $^{67}\text{Ga}$ -binding glycoprotein from a rat hepatoma. *Cancer Res.* 38:4440-4444, 1978.

Hubner, K.F., Andrews, G.A., Buonocore, E., Hayes, R.L., Washburn, L.C., Collmann, I.R., and Gibbs, W.D. Carbon-11-labeled amino acids for the rectilinear and positron tomographic imaging of the human pancreas. *J. Nucl. Med.* 20:507-513, 1979.

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., Butler, T.A., and Callahan, A.P. High-level production of C-11-carboxyl-labeled amino acids. In Radiopharmaceuticals II, proceedings of 2nd International Symposium on Radiopharmaceuticals, Seattle, Wash., 1979, pp. 767-777.

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Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. [Carboxyl- $^{11}\text{C}$ ] l-aminocyclobutanecarboxylic acid, a potential tumor-seeking agent. *J. Nucl. Med.* 20:1055-1061, 1979.

Hayes, R.L., Rafter, J.J., and Byrd, B.L. Studies of the mechanism of gallium-67 uptake by tumor, abscess and normal tissues. *J. Nucl. Med.* 20:672-673, 1979 (abstr.).

Hayes, R.L., Szymendera, J.J., and Byrd, B.L. Effect of food intake on the tissue distribution of gallium-67: Concise communication. *J. Nucl. Med.* 20:938-940, 1979.

Hayes, R.L., Byrd B.L., Rafter, J.J., and Carlton, J.E. The effect of scandium on the tissue distribution of Ga-67 in normal and tumor-bearing rodents. *J. Nucl. Med.* 21:361-365, 1980.

Casey, D.L., Digenis, G.A., Wesner, D.A., Washburn, L.C., Chaney, J.E., Hayes, R.L., and Callahan, A.P. Preparation and preliminary tissue studies of optically active C-11-D- and L-phenylalanine. *Int. J. Appl. Radiat. Inst.* (in press)

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BIOGRAPHICAL SKETCH

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator Program Director. Photocopy this page for each person.

NAME	TITLE	BIRTH DATE (Mo., Day, Yr.)	
Paul Harvey King		[REDACTED]	
EDUCATION (Begin with baccalaureate training and include postdoctoral)			
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- 6/61-6/62 Case Institute of Technology (Asst. in Accelerometer Research), Cleveland, OH.
- 6/62-9/62 Bell Aerosystems Co., (accelerometer research and design), Cleveland, OH.
- 9/62-9/65 Highland View Hospital (Metabolic Ward), Cleveland, OH.
- 12/66-9/69 Kidney Dialysis Unit, Veteran's Hospital, Nashville, TN.
- 2/66-present Nuclear Medicine Department, Vanderbilt Hospital, Nashville, TN.
- 8/69-present Vanderbilt and Veterans Hospital, Dynamics of bone healing, gait analysis.
- 2/71-present Vanderbilt and Veterans Hospital, Vectorcardiography research.
- 1972-present Associate Professor, Vanderbilt University, Nashville, TN.
- 7/78-7/79 Sabbatical-Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN. (Presently a consultant)

Honors: American Men & Women of Science - General (1973) and Medical Sciences (1975); Skylab Award - 1975; Skylab Achievement Award 1975; Group Achievement Award, Skylab Medical Team 1975; Directory of International Biography 1976; Who's Who in the South and Southwest 1979.

Publications:

- King, P.H., and Apple, H. Computer Oriented Study of Metabolism, Data Acquisition and Processing in Biology and Medicine, Paragamon Press, Vol. 4, 1964, pp. 23-36.
- King, P.H. Numerical Analysis and Data Processing in Metabolism Research. Master's Thesis, Case Institute of Technology, Cleveland, OH, 1965.
- King, P.H. Brill, A.B., and King, R.J. Computer applications in nuclear medicine. J. Nucl. Med. 7:803, 1966.
- King, P.H., Baker, W., Day, R., Greenway, R., Lindan, O., and Reswick, J. Measurement of the random component ("noise") in the study of short-term fluctuations in urine composition. In 19th Annual Conference on Engineering in Medicine and Biology, San Francisco, Calif., November 1966, Vol. p. 203.
- Patton, J., Brill, A.B., Erickson, J., and King, P.H. Cylindrical array tomographic scanner with focusing collimators and its possible adaptation for fluorescence scanning of brain tumors. Sou. Med. J. 62:1434, 1969.
- Brill, A.B., Johnston, R.E., Davies, H., King, P.H., Erickson, J., Williams, H., and Nash, R. Analysis of imaging techniques using digitally simulated scans. Sou. Med. J. 62, 1969.

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Patton, J., Brill, A.B., and King, P.H. Transverse section brain scanning with multi-crystal cylindrical imaging device. Conference on Radionuclide Tomography, Sept. 15, Tomographic Imaging in Nuclear Medicine. Society of Nuclear Medicine, New York, 1973, pp. 28-43.

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Smith, R.F., King, P.H., Stanton, K., Stoop, D., and Brown, D. Quantitative electrocardiography during extended spaceflight. The first skylab mission. *Astronautica Acta* 2:89-102, 1975.

Smith, R.F., Stanton, K., Stoop, D., Janusz, W., and King, P.H. Quantitative electrocardiography during extended spaceflight: The second skylab mission. *Aviation, Space and Environmental Medicine*, April 1976, pp. 353-359.

Smith, R.F., Stanton, K., Stopp, D., Brown, D., and King, P.H. Quantitative electrocardiography during extended spaceflight. *Basic Environmental Problems of Man in Space*, Ashton Graygiel, ed., Pergamon Press, 1976, pp. 89-102.

Wieland, B.W., Highfill, R.R., and King, P.H. Proton accelerator targets for the production of  $^{11}\text{C}$ ,  $^{13}\text{N}$ ,  $^{15}\text{O}$ , and  $^{18}\text{F}$ . *IEEE Transactions on Nuclear Sciences*, Vol NS-26(1):1713-1717, 1979.

King, P., Hübner, K.F., Gibbs, W.D., and Holloway, E. Noise identification and removal in positron imaging systems. In Proceedings of IEEE-Transactions on Nuclear Science, February, 1981. (in press)

Hubner, K.F., King, P., Gibbs, W.D., Washburn, L.C., and Hayes, R.L. Positron emission computerized tomography: A potential tool for in vivo quantitation of the distribution of radiopharmaceuticals. In Proceedings of the Third International Radiopharmaceutical Dosimetry Symposium, Oak Ridge, TN October 7-10, 1980. (in press)

Paul H. King has 34 other publications, abstracts, and presentations.

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**BIOGRAPHICAL SKETCH**

Give the following information for key professional personnel listed on page 2, beginning with the Principal Investigator Program Director. Photocopy this page for each person.

NAME I. Reid Collmann	TITLE Clinical Professor of Medicine	BIRTHDATE Mo., Day, Yr. [REDACTED]	
EDUCATION (Begin with baccalaureate training and include postdoctoral)			
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Include present membership on any Federal Government Public Advisory Committee. List, in chronological order, the titles and complete references to recent representative publications, especially those most pertinent to this application. Do not exceed 2 pages.

- 1954-1965 Captain, MC, U. S. Army, 2nd General U. S. Army Hospital, Lanstuhl, W. Germany.
- 1965-present Chief, Department of Gastroenterology, University of Tennessee Memorial Research Center & Hospital, Knoxville, Tennessee.
- 1966-present Clinical Professor of Medicine, University of Tennessee Memorial Research Center & Hospital, Knoxville, Tennessee.

Honors: Membership in Medical Societies: A.S.G.E., AMA, A.S.I.M., S.M.A., Knoxville Academy of Medicine.

Publications

- Peirce, E.C., II, Leshner, J.H., Law, W., and Collmann, I.R. Chronic occlusion of aortic arch branches. Dis. Chest 36:542-551, 1959.
- Lange, R.D., Chernoff, A.I., Jordan, T.A., and Collmann, I.R. Experience with a hemagglutination-inhibition test for carcinoembryonic antigen: preliminary report. In Proceedings of the First Conference and Workshop on Embryonic and Fetal Antigens in Cancer, N.G. Anderson and J.H. Coggin, Jr., eds., 1971, pp. 379-386.
- Andrews, G.A., Hübner, K.F., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Collmann, I.R. Clinical studies of C-11-labeled amino acids. J. Nucl. Med. 18:638, 1977 (abstr.).
- Buonocore, E., Hübner, K.F., and Collmann, I.R. Differentiation of retroperitoneal tumor using positron emission computed tomography. J. Comput. Asst. Tomogr. 3(6):825-828, 1979.
- Hübner, K.F., Andrews, G.A., Buonocore, E., Hayes, R.L., Washburn, L.C., Collmann, I.R., and Gibbs, W.D. Carbon-11-Labeled amino acids for the rectilinear and positron tomographic imaging of the human pancreas. J. Nucl. Med. 20:507-513, 1979.

## OTHER SUPPORT

(USE CONTINUATION PAGES IF NECESSARY)

For each of the professionals named on page 2, list, in three separate groups: (1) active support; (2) applications pending review and/or funding; (3) applications planned or being prepared for submission. Include all Federal, non-Federal, and institutional grant and contract support. If none, state "NONE." For each item give the source of support, identifying number, project title, name of principal investigator/program director, time or percent of effort on the project by professional named, annual direct costs, and entire period of support. (If part of a larger project, provide the titles of both the parent grant and the subproject and give the annual direct costs for each.) Briefly describe the contents of each item listed. If any of these overlap, duplicate, or are being replaced or supplemented by the present application, justify and delineate the nature and extent of the scientific and budgetary overlaps or boundaries.

## PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR:

## (1) ACTIVE SUPPORT:

DOE Contract #DE-AC05-76OR00033, "Clinical Radiopharmaceutical Development", Dr. Karl F. Hübner: Principal Investigator, 10% effort, \$110,000 Annual Direct Costs, Period of Support 10/1/80-9/30/81. Program is involved in the preliminary clinical evaluation of newly developed radiopharmaceuticals.

DOE Contract #DE-AC05-76OR00033, "Radiation Emergency Assistance Center/Training Site", Dr. Karl F. Hübner, Principal Investigator, 90% effort, \$650,000 Annual Direct Costs, Period of Support 10/1/80-9/30/81. This program involves the ability to receive and care for radiation accident victims, the training of physicians, EMTs and paramedics in radiation accident handling and research of physical effects of radiation exposure.

(2) APPLICATIONS PENDING: None

## (3) APPLICATIONS PLANNED:

Resubmission of revised NIH Grant #CA29490-01, "C-11-Amino Acids/Positron ECT for Pancreatic Studies," Dr. Karl F. Hübner: Principal Investigator, 20% effort, \$75,750 Annual Direct Costs, 07/01/81-06/30/82, \$243,400 Total Direct Costs, 07/01/81-06/30/84.

This program does duplicate studies listed in "Clinical Radiopharmaceuticals" (1) above, but rather extends our evaluation of amino acids by the use of positron tomography to a complete study of compounds centering on localization in the pancreas.

**OTHER SUPPORT**  
(USE CONTINUATION PAGES IF NECESSARY)

For each of the professionals named on page 2, list, in three separate groups: (1) active support; (2) applications pending review and/or funding; (3) applications planned or being prepared for submission. Include all Federal, non-Federal, and institutional grant and contract support. If none, state "NONE." For each item give the source of support, identifying number, project title, name of principal investigator/program director, time or percent of effort on the project by professional named, annual direct costs, and entire period of support. (If part of a larger project, provide the titles of both the parent grant and the subproject and give the annual direct costs for each.) Briefly describe the contents of each item listed. If any of these overlap, duplicate, or are being replaced or supplemented by the present application, justify and delineate the nature and extent of the scientific and budgetary overlaps or boundaries.

## PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR:

## (1) ACTIVE SUPPORT:

DOE Contract #DE-AC05-76OR00033, "Preclinical Radiopharmaceutical Development"  
Dr. R. L. Hayes: Principal Investigator, 100% effort, \$260,000 Annual Direct Costs, 10/0-/80-09/30/81. (Only Dr. Washburn's salary and benefits are supported under this program. Dr. Washburn does not have individual research support.)

(2) APPLICATIONS PENDING: None

(3) APPLICATIONS PLANNED: None

## RESOURCES AND ENVIRONMENT

FACILITIES: Mark the facilities to be used and briefly indicate their capacities, pertinent capabilities, relative proximity and extent of availability to the project. Use "other" to describe facilities at other performance sites listed in Item 9, page 1, and at sites for field studies. Using continuation pages if necessary, include a description of the nature of any collaboration with other organizations and provide further information in the RESEARCH PLAN.

- Laboratory: Our equipped radiopharmaceutical development research space consists of 2 large (750 sq. ft. each) and 2 smaller laboratories (500 sq. ft. each), all with fume hoods. A positive pressure "clean room" with 2 vertical laminar flow benches (1 recirculating, 1 exhaust) is available for final preparation of labeled materials before administration to patients.
- Clinical: Clinical tests will be carried out at the Oak Ridge Associated Universities Medical and Health Sciences Division facilities in Oak Ridge. The patients will come from referring physicians at the Oak Ridge Hospital, the Knoxville hospitals, and other nearby institutions such as Vanderbilt University. The Medical and Health Sciences Division has a long history of cooperation with referring physicians and demonstrated ~~xxxxxxx~~ ability to attract patients for experimental work. All proposed clinical studies will receive prior approval from the ORAU Human Studies Committee and the U.S. Food and Drug Administration before they are carried out in patients. Informed consent will be obtained for each study.
- Computer: Computer capability included in ECAT-II tomograph.
- Office: Routine secretarial services.
- Other (Cyclotron Complex): The Oak Ridge National Laboratory's 22 MeV, 86-inch proton cyclotron is available. An alteration to the cyclotron which will permit rapid, remote changing of targets is to be installed in the spring of 1981. A hot cell with power-assisted manipulators is located approximately 50 ft. from the cyclotron.

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location, and pertinent capabilities of each. The following major equipment is already available at the Medical and Health Sciences Division of ORAU: ORTEC ECAT II whole body positron emission computerized tomograph; 2 HPLC chromatographs; HPLC radioactivity, refractive index, and variable wavelength UV detectors; HPLC gradient generator and strip chart recorder with computing integrator.

ADDITIONAL INFORMATION: Provide any other information describing the environment for the project. Identify support services such as consultants, secretarial, machine shop, and electronics shop, and the extent to which they will be available to the project. The surrounding scientific institutions employ many individuals who are now and can in the future be helpful in a variety of ways. Of these the Nuclear Medicine Technology Group at the Oak Ridge National Laboratory is the closest at hand and the University of Tennessee with its various disciplines and departments as well as the Memorial Research Center is nearby in Knoxville. A variety of basic and clinical disciplines are represented at the Medical and Health Sciences Division itself, i.e., pathology, cytogenetics, radiobiology, ultrastructural anatomy, biochemistry, and immunology.

## SUMMARY OF INVESTIGATORS' RESPONSE TO CRITIQUE

The grant application has been revised in accordance with the critique of the review committee. The budget has been amended as suggested in the critique.

The need for  $^{11}\text{C}$ -labeled natural amino acids (L-isomers) for studies of amino acid metabolism in the brain, as well as for the proposed pancreatic studies, has led us to proceed with efforts directed toward resolution of  $^{11}\text{C}$ -labeled amino acid racemates under our U.S.D.O.E.-supported program. Successful resolution of both  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine on an analytical scale has been accomplished by high pressure liquid chromatography. Scale-up of this procedure to a preparative scale should produce  $^{11}\text{C}$ -L-tryptophan and  $^{11}\text{C}$ -L-valine in quantities sufficient for the proposed clinical studies. These agents should be available for clinical use by the start of the second grant year. It should be emphasized that the development of resolution techniques will be supported from U.S.D.O.E. funds. The proposed grant would support production of the radiopharmaceuticals for clinical use.

In accordance with the deletion of support for resolution development and as suggested in the critique, one of the research associate positions and the secretary position have been dropped. In addition, projected salary increases for the next calendar year have been included. Therefore, in order to remain close to the critique's personnel figure, Dr. Washburn's time on the grant has been reduced from 20% to 10%.

Since funds for updating the ECAT-I to an ECAT-II have been obtained from the U.S.D.O.E., we have, of course, deleted funds for equipment. As suggested in the critique, we have reduced travel funds from \$2,300 to \$1,700 with the specific reduction being in staff rather than consultant travel. The budget reduction in the category of other expenses has been met by deleting support for A. P. Callahan (ORNL) from the grant. This will mean retention of all the funds for cyclotron time, ensuring sufficient funding for the proposed work. In accordance with NCI policy, increases in funds for the second and third grant years have been reduced to 6%.

Some of the points and questions raised in the critique need to be clarified. First, the statement was made that the proposed study is limited almost entirely to tryptophan, valine, ACPC, and ACBC, and that the development of pancreas specific agents and studies using  $^{14}\text{C}$  are not covered. Such studies have already been done. Animal studies by both our research group and others have shown that tryptophan is by far the most pancreas specific of all the naturally occurring amino acids. Valine is probably the second best. This also seems to be true in the clinical studies done to date, although a few more cases are needed to substantiate this claim.

Potential problems with liver interference were raised. Actually because of the high pancreas-to-liver ratios obtained with our agents (approximately 5:1 for  $^{11}\text{C}$ -DL-tryptophan) and the use of transaxial imaging with positron ECT, liver interference has not been a problem.

It was stated that the desirability of determining whether DL-tryptophan or DL-valine is the best is not clear since neither racemic mixture shows

normal/tumor selectivity. It is true that it would be preferable to use  $^{11}\text{C}$ -L-tryptophan and  $^{11}\text{C}$ -L-valine in such a comparison, and the early availability of the resolved amino acids may permit this to be done.

The potential use of  $^{11}\text{C}$ -labeled D-amino acids for tumor imaging was mentioned. This is a distinct possibility for some tumor types, and we are very interested in investigating it. However, D-amino acids are also taken up by the normal pancreas, and thus differential diagnosis of pancreatic carcinoma using  $^{11}\text{C}$ -labeled D-amino acids would not be practical.

The possibility of using  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC alone as imaging agents was brought up. Diagnosis of tumors should be possible using this technique, but it would be impossible to distinguish pancreatic carcinomas from other types of abdominal tumors. Use of  $^{11}\text{C}$ -L-tryptophan or  $^{11}\text{C}$ -L-valine in conjunction with  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC would permit a differential diagnosis to be made. That is, a pancreatic tumor would appear as a defect in the normal pancreatic image.

Since submission of the first version of this proposal, progress has been made towards improved quantitative in vivo application of positron emission computerized tomography. Image noise from "randoms" and scattered events has been characterized mathematically as a convolving process and a deconvolution equation has been developed and transferred into a soft-ware program compatible with the PDP 11/45 computer of the ECAT-I systems. In phantom studies we have shown that noise removal from the data prior to image reconstruction improves quantitative data analysis in the final images to within 10% of the true data (this work is in print, note added references 35 and 36 on the last page of this new proposal). In the first half of calendar year 1981, we will make every effort to transfer the noise correction schemes of Dr. Paul King into the ECAT-II computer system so that adequate quantitation as proposed in this grant application should be possible quite early during the period for which funding is being requested.

The last point raised in the critique pertaining to diagnostic tests is well taken. The "clinical information required" as outlined in Table 3 of the original proposal is redundant, and we certainly did not intend to get funding for all these tests. Rather the table was meant to indicate what kind of studies and tests might have supported the diagnosis (or suspicion) of pancreatic cancer or pancreatitis in one or the other patient. Since the information given in the table is not relevant to the proposed work, the table has been deleted and is being replaced by a short statement: "The routine conventional diagnostic tests to support the suspicion or diagnosis of pancreatic disease are not expected to be paid for by this grant."

Continuation page

## RESEARCH PLAN

A. Specific Aims

Our overall objective is to evaluate the potential of using  $^{11}\text{C}$ -labeled natural and unnatural amino acids in conjunction with positron emission computerized tomography for the non-invasive differential diagnosis of pancreatic disease.

In selected patients with suspected cancer of the pancreas, the uptake and distribution of  $^{11}\text{C}$ -labeled L-tryptophan or L-valine will be studied tomographically in order to determine whether in man the L-isomer localizes to a higher degree in normal pancreatic tissue than in neoplastic lesions of the pancreas, pancreatitis, pancreatic cysts, and benign tumors. (We have observed that DL-mixtures localize in both normal pancreas and in pancreatic carcinoma.) Success on an analytical scale has recently been achieved in the rapid resolution of the  $^{11}\text{C}$ -labeled DL-racemates by high pressure liquid chromatography (HPLC). We anticipate that the scale-up of this procedure to a preparative HPLC column will be completed during the first grant year. (Funding for this development work will not come from the proposed grant.) This will make available  $^{11}\text{C}$ -labeled L-tryptophan and L-valine for the proposed studies.

These same patients will also be examined with either  $^{11}\text{C}$ -l-aminocyclopentane-carboxylic acid ( $^{11}\text{C}$ -ACPC) or  $^{11}\text{C}$ -l-aminocyclobutanecarboxylic acid ( $^{11}\text{C}$ -ACBC), alicyclic unnatural amino acids that we have identified as tumor-localizing agents. The choice will be based on a determination in man of the agent having the higher uptake in pancreatic tumors relative to that in normal pancreas. Therefore, this research will test the potential of using  $^{11}\text{C}$ -labeled L-tryptophan or L-valine in conjunction with  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC for the complete differential diagnosis of pancreatic disease by positron tomography.

A further aim of this proposed work is to develop and test methods for the quantitative analysis of the in vivo distribution of  $^{11}\text{C}$ -labeled natural and unnatural amino acids in normal pancreas and specific sites of pancreatic disease. We propose to measure quantitatively amino acid extraction by pancreatic neoplasms before, during, and after chemotherapy or radiation therapy, i.e., to develop a model system for objectively gauging response of pancreatic tumors to therapy based on metabolic parameters rather than standard radiographic or subjective clinical evaluations.

B. Significance

Carcinoma of the pancreas is now the fourth leading cause of death among cancer patients (1). It is usually diagnosed at an advanced stage. Although not yet proven, it is reasonable to assume that the prognosis for patients with cancer of the pancreas could be improved through earlier diagnosis and treatment.

The development of computer-assisted tomography (CT) and ultrasound (US) have greatly improved the diagnostic assessment of pancreatic carcinoma, although the diagnostic accuracy is not better than 84% for CT and 80% for US, as was shown by Husband et al (2). Other US studies by Feinberg et al (3) gave accurate diagnostic information in 93.8% of the cases. Haaga et al (4) diagnosed pancreatic neoplasms with CT correctly in 28 of 32 cases whereas US was incorrect in 3 of 7 patients. The accuracy of US in diagnosing pancreatic carcinoma varies considerably from laboratory to laboratory, but nevertheless US seems to be quite helpful as a screening method.

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Continuation page

Research Plan: Significance (continued)

A nuclear medical technique employed with some success for diagnosis of pancreatic carcinoma involves imaging of the pancreas with a modified amino acid,  $^{75}\text{Se}$ -labeled L-selenomethionine. The pancreas is known to have a selective avidity for many amino acids (5). The use of a modified methionine is, however, not based on its avidity for pancreas so much as on the fact that methionine contains a sulfur atom which can be replaced by the gamma-emitting radionuclide  $^{75}\text{Se}$  without greatly altering the localization of the amino acid in the pancreas (6). With this technique cancers of the pancreas are seen as areas of decreased or absent uptake when the organ is visualized, usually by  $^{99\text{m}}\text{Tc}$ -colloid liver subtraction techniques (7). The procedure has been successful enough to become rather widely adopted, but it is far from ideal for several reasons: (1) the normal variability in the shape and position of the pancreas, (2) the presence of overlying organs anteriorly and posteriorly, (3) poorly explained variabilities in radiopharmaceutical concentration in the organ (in spite of various dietary regimens), and (4) high radiation dose to the patient due to the long physical half-life of  $^{75}\text{Se}$  (120 days) and the long biologic half-time of the agent (70 days). The general consensus appears to be that  $^{75}\text{Se}$ -L-selenomethionine scanning of the pancreas does not significantly contribute to the early diagnosis of cancer of the pancreas (8,9). Other extrastructurally labeled amino acids such as  $^{123}\text{I}$ -4-iodophenylalanine (10),  $^{123}\text{I}$ -5- and 6-iodotryptophan (10), and  $^{18}\text{F}$ -5- and 6-fluorotryptophan (11) have been synthesized but have not appeared to be promising pancreas-scanning agents.

The use of radiopharmaceutical agents labeled with positron-emitting short-lived radionuclides makes possible external detection by coincidence counting techniques such as positron emission computerized tomography, which has the advantages of improved resolution and localization independent of depth. This approach offers a new non-invasive in vivo probe for quantitative and metabolic studies in man. It is particularly appealing because metabolic precursors and physiologically active compounds can be labeled with  $^{11}\text{C}$  ( $T_{1/2} = 20$  min) or  $^{13}\text{N}$  ( $T_{1/2} = 10$  min) without changing their biological properties; therefore, accurate external physiologic and metabolic observations that are otherwise only possible by autoradiography ( $^{14}\text{C}$ ,  $^3\text{H}$ ) or other invasive analyses of excised tissue can be made. Furthermore, the use of short-lived radionuclides permits sequential examinations over short time intervals without undue radiation exposure to the patient.

The work proposed in this application involves the use of  $^{11}\text{C}$ -labeled amino acids in the diagnosis of pancreatic diseases by positron emission computerized tomography. Although most naturally occurring amino acids show a significant affinity for the pancreas, two of them, tryptophan and valine, appear from animal studies to have the highest degree of pancreatic specificity (5, 12-14).

Washburn, Hayes, and co-workers of this laboratory have developed methods for synthesizing  $^{11}\text{C}$ -labeled amino acids (15,16), and ours is at present the only laboratory in the United States that has used these agents in positron tomographic clinical investigations. The production method, a rapid, high-temperature, high-pressure modification of the Bücherer-Strecker amino acid synthesis, gives racemic mixtures of  $^{11}\text{C}$ -labeled amino acids. (Reference 16, attached as Appendix A, gives details of the method.)

Up to this point our clinical experience with  $^{11}\text{C}$ -labeled tryptophan and valine has been restricted to the DL racemates (17,18) because resolution methods rapid enough to be compatible with the 20.4 min  $T_{1/2}$  of  $^{11}\text{C}$  have only recently begun to be developed for these amino acids. No method that allows direct  $^{11}\text{C}$ -labeling of the L-forms of valine and tryptophan has been devised.

Continuation page

Research Plan: Significance (continued)

In order to accomplish the main task of this proposal, namely to make a significant contribution to the differential diagnosis of pancreatic diseases, it is of utmost importance to use the L-isomer of either  $^{11}\text{C}$ -labeled tryptophan or valine for positron tomography of the pancreas. The optical isomers of amino acids show distinctly different behaviors in cancer and normal pancreatic tissue. Tamemasa (19) has shown that the L-isomers have a high affinity for normal pancreas, whereas the D-forms tend to localize preferentially in neoplastic lesions. Therefore, the DL-form would be expected to share the characteristics of both enantiomers and concentrate in normal pancreas and in pancreatic tumors to an approximately equal degree. We have observed such behavior with  $^{11}\text{C}$ -DL-tryptophan in our preliminary clinical studies. Thus by using the L-optical form of tryptophan or valine, we should be able to distinguish between functioning normal pancreas and any disease processes that are present. Malignant lesions could then be differentiated from benign, cystic, and inflammatory processes by using either  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC, alicyclic unnatural amino acids that show preferential uptakes in tumor tissue but no affinities for inflammatory lesions (20). This non-invasive technique could thus provide for the complete differential diagnosis of pancreatic diseases, hopefully at an early stage.

Recent studies by Comar and co-workers (21) with  $^{11}\text{C}$ -L-methionine and positron tomography show that neoplastic lesions of the pancreas do appear as defects in the normal pancreatic image. (The production method for  $^{11}\text{C}$ -L-methionine, methylation of L-homocysteine with  $^{11}\text{CH}_3\text{I}$ , is not applicable to other  $^{11}\text{C}$ -labeled amino acids.) These findings, coupled with our own observations and published reports, have prompted our interest in using  $^{11}\text{C}$ -labeled L-tryptophan or L-valine as differential pancreas-scanning agents in conjunction with  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC.

In collaboration with Dr. G. Digenis of the University of Kentucky, we have successfully resolved  $^{11}\text{C}$ -DL-phenylalanine into its D- and L-isomers by oxidative deamination using immobilized L- and D-amino acid oxidase, respectively (22). The yields for  $^{11}\text{C}$ -D- and L-phenylalanine were 19 mCi and 27 mCi. Purification was accomplished by cation exchange chromatography, and the optical purity was established by optical rotatory dispersion. Resolution and purification required 35 minutes.

Several reports (23-26) have appeared recently concerning direct resolution of amino acid enantiomers by high pressure liquid chromatography (HPLC), and the technique seems ideal for resolution of  $^{11}\text{C}$ -labeled amino acids. We have recently succeeded in resolving both  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine on an analytical scale using high pressure liquid chromatography (see Methods) (27). Scale-up of this procedure to a preparative column should produce  $^{11}\text{C}$ -L-tryptophan and  $^{11}\text{C}$ -L-valine in sufficient quantity for the proposed clinical studies. The potential advantages of this method are its speed of separation and the fewer manipulations that are required relative to the enzymatic method.

The success of the project depends on the availability of  $^{11}\text{C}$ -amino acid racemates, but equally important is the development of computer capability and the acquisition of an updated ECAT scanner (equivalent to ECAT II). The installation of the ECAT-II system (funded by the U.S. DOE) is currently in progress and is expected to be completed prior to the start of the proposed project. Correct staging of malignant tumors and objective evaluation and measurement of the response of tumors to therapy is not always possible. It is especially difficult to measure regression of tumors early after initiation of therapy, and a method that allows objective external measurement of biological/metabolic changes induced by treatment would be

Research Plan: Significance (continued)

highly desirable. In this proposed research we will attempt to develop a biologic "caliper" to measure pancreatic tumor response to therapy by using quantitative positron emission computerized tomography to measure the fraction of  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC extracted by a tumor. This kind of test would be an extremely useful research tool for monitoring therapy, and it could be the basis for a simple test using an external counting method less sophisticated and less expensive than positron tomography.

C. Preliminary Studies

On the basis of the partial success of diagnostic procedures with radiopharmaceuticals such as  $^{75}\text{Se}$ -L-selenomethionine, we have undertaken to try a series of related diagnostic methods that take advantage of several potential improvements:

(a) As stated above, certain amino acids show a greater tendency to concentrate in the pancreas than does  $^{75}\text{Se}$ -L-selenomethionine. In animal work carried out by ourselves (13,14) and others (5,12), both DL-tryptophan and DL-valine have been shown to have a high affinity for the pancreas. We have shown that these  $^{11}\text{C}$ -labeled amino acids can be rapidly synthesized and purified in quantities adequate for pancreas visualization in animals and man (15,16). Table 1 shows our production experience for the four  $^{11}\text{C}$ -labeled amino acids discussed in this proposal. (The method is quite general and is useful for production of many other  $^{11}\text{C}$ -labeled amino acids.) We are able to produce multiple batches of  $^{11}\text{C}$ -labeled amino acids at intervals of 1 hr or less by overlapping the various steps, i.e., generation of  $^{11}\text{C}$  activity, amino acid synthesis, amino acid purification, and column regeneration. In a typical all-day run, we routinely produce four or more batches of various  $^{11}\text{C}$ -labeled amino acids for clinical or preclinical investigation.

Table 1  
 $^{11}\text{C}$ -Labeled Amino Acid Production at M&HSD/ORAU  
(Through October 15, 1980)

Amino Acid	Total Number Batches	Number Patient Studies	Total Activity (mCi)	Average mCi/batch	Highest Yield (mCi)
$^{11}\text{C}$ -DL-Valine	49	28	8,260	170	360
$^{11}\text{C}$ -DL-Tryptophan	74	67	9,110*	123	330
$^{11}\text{C}$ -ACPC	79	62	7,952*	101	300
$^{11}\text{C}$ -ACBC	54	50	7,665	142	420

\* In early development of these compounds the total yield was almost zero, so total activity and average per batch were quite low.

(b) We can take advantage of the special radiation characteristics of  $^{11}\text{C}$ . Decay by positron emission is accompanied by the production of two annihilation photons emitted at an angle of  $180^\circ$  to each other. Using recently developed instrumentation that utilizes these coincident annihilation photons and the techniques associated with transmission computerized tomography, it is possible to reconstruct cross-sectional images that show three dimensionally the source of positron-emitting activity in the body (28, 29). The distinct advantage of this type of imaging is

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Research Plan: Preliminary Studies (continued)

that it provides high resolution and avoids image distortion due to overlying radioactivity and that the image is subject to quantitative analysis (30). The Medical and Health Sciences Division of Oak Ridge Associated Universities has applied a commercially available positron emission computerized tomographic scanner (ECAT I) to clinical investigations since May 1977. By combining the advantages of  $^{11}\text{C}$ -labeled DL-tryptophan or DL-valine with this optimal type of imaging, it was anticipated that greatly improved pancreatic diagnostic results could be obtained. Carcinomas were expected to be seen as zones of decreased or absent concentration as is the case with  $^{75}\text{Se}$ -L-selenomethionine.

(c) Based on this concept, we also developed a method for labeling the unnatural alicyclic amino acids l-aminocyclopentanecarboxylic acid (ACPC) and l-aminocyclobutanecarboxylic acid (ACBC) with  $^{11}\text{C}$  because of their potential as tumor-localizing agents, particularly when used in conjunction with positron tomography (31,32). Thus  $^{11}\text{C}$ -ACPC and  $^{11}\text{C}$ -ACBC were developed for confirmatory studies on malignancies suspected on  $^{11}\text{C}$ -DL-tryptophan or  $^{11}\text{C}$ -DL-valine pancreas scans.

Our results have shown that positron tomographic imaging of the pancreas with  $^{11}\text{C}$ -carboxyl-labeled DL-tryptophan and DL-valine allows physiologic studies by imaging and has the potential to measure in vivo the utilization of metabolic substrates or analogs. Positron tomographic studies (examples are shown in Appendix B) supplement the morphologic information obtained by ultrasound (US) and transmission computerized tomography (CT). A group of 29 patients with proven or suspected pancreatic disease was examined with positron ECT; 18 of these subjects were also studied with US and transmission CT. In 26 patients with known clinical outcomes, positron tomography gave one false positive and three false negative results (17). Ultrasound and/or transmission CT failed to show three proven lesions. Increased uptake of  $^{11}\text{C}$ -DL-tryptophan delineated three pancreatic carcinomas and one lymphoma. In normal subjects positron tomography with these agents invariably showed the pancreas with striking clarity. These observations indicate that positron tomography provides a unique method for visualizing biologic activity and that quantitative analysis of amino acid utilization should be possible with this non-invasive technique. The fact that selective pancreatic localization of these agents occurs almost immediately after intravenous injection means that the short half-life of  $^{11}\text{C}$  rather than being a disadvantage is on the contrary actually an asset in terms of lowered radiation dose and the possibility of frequent repetition of scans.

We have shown the general usefulness of the unnatural amino acid  $^{11}\text{C}$ -ACBC as a tumor-localizing agent in conjunction with positron tomography. Our present experience with  $^{11}\text{C}$ -ACBC is limited to 33 patients. The variety of neoplasms that concentrate  $^{11}\text{C}$ -ACBC very rapidly after intravenous injections includes bronchogenic carcinoma, metastatic mammary Ca, lymphomas (33), and poorly differentiated carcinomas, as well as cancer of the pancreas.  $^{11}\text{C}$ -ACBC cannot be metabolized and shows promise as a useful tool for measuring the metabolic activity and/or the proliferative stage of tumor tissues.

Our finding that the racemic forms of  $^{11}\text{C}$ -valine and  $^{11}\text{C}$ -tryptophan localized to a significant degree in pancreatic neoplasms was unexpected. We had expected to see carcinomas as zones of decreased or absent concentration as is the case with  $^{75}\text{Se}$ -L-selenomethionine. Especially in view of findings published by Tamemasa et al (19), it is likely that the presence of the D isomer is responsible for the tumor affinity observed with the amino acid racemates we used in our studies.

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Research Plan: Preliminary Studies (continued)

A crucial factor involved in the success of the proposed project involves quantitation using an ECAT positron emission computerized tomograph. In the course of over 3 years experience in patient studies and intentional computer program challenges in phantom studies, we have observed some serious deficiencies in the performance of our ECAT; i.e., phantom studies indicate that reconstructed data, in terms of calculated image "quantity" versus "dose", is not a linear function. The amount of isotope measured in a particular region of a reconstructed image is both a function of the image size (34) and the amount of isotope present (a non-linear function, due to randomness)! The "measured" amount of activity in an area, as a function of time, if the effect of count rate were to be ignored, is of little significance in the pancreas, as the size of that organ does not change significantly. However, the ability of the pancreas to extract the various labeled agents which we propose to use, and therefore the relative amount of Compton and random scatter contributing to a calculation of relative isotope uptake, will influence our measurement of the rate of suppression (or lack thereof) of the cancerous tissues' growth. Our experience with calculations on phantoms has dramatically shown the effect of both image size (equivalent in part to tumor size) and count rate (equivalent to tumor uptake) on quantification of our results. A 30% or greater variation in count rate per cm<sup>2</sup> has not been uncommon in our data, despite efforts to correct the data for known non-linearities.

We have improved on the basic software provided with the original ECAT I system, initiating procedures involving multi-level transmission image data correction, Compton scatter correction, outlier data squelching, background subtraction routines, etc., but we are still in need of better data, as collected, to quantify and confidently analyze our results.

A new version of the ECAT, ECAT II, overcomes to a great extent the problems we have encountered with our ECAT I. We, therefore, are *in the process of updating our ECAT I electronically to an ECAT II, and this work should be completed prior to the start of the project.*

#### D. Methods

##### Resolution of <sup>11</sup>C-labeled amino acids

An essential part of this proposal is the development of synthetic techniques for rapidly resolving the racemic mixtures of <sup>11</sup>C-labeled amino acids which result from the modified Bücherer-Strecker synthesis. Our production method (16) has produced up to 330 mCi of <sup>11</sup>C-DL-tryptophan and 360 mCi of <sup>11</sup>C-DL-valine in a total synthesis and purification time of 40-45 min, one-half of which is devoted to synthesis and the other half to chromatographic purification. (See Appendix A for details.) Because of our high production capability, we should, therefore, be able to separate the L-isomers from these racemates and still have more than an adequate amount of <sup>11</sup>C-labeled L-tryptophan or L-valine for clinical studies (~ 10-15 mCi will be required).

We propose to combine resolution and purification through use of recently developed chromatographic techniques. This should result in an overall synthesis, resolution, and purification time which is compatible with the 20.4 min half-life of <sup>11</sup>C. This production time could, in fact, be no longer than the 40-45 min currently required for <sup>11</sup>C-labeled racemic amino acids.

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Research Plan: Methods (continued)

Based on our preliminary clinical studies using  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine (see Preliminary Studies) and animal studies by both our group (13,14) and others (5,12), tryptophan appears to be considerably more specific for the pancreas than valine. Proposed studies during the first year of support will further compare the two agents (see following section on proposed clinical investigations). If  $^{11}\text{C}$ -DL-tryptophan is indeed shown to be superior, our resolution efforts will be concentrated on this agent.

The method of choice for resolution of  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine appears to be high pressure liquid chromatography (HPLC). Since  $^{11}\text{C}$ -labeled natural amino acids are greatly needed for studies of amino acid metabolism in the brain, as well as for the proposed pancreatic studies, we have proceeded with efforts directed towards resolution of  $^{11}\text{C}$ -labeled amino acid racemates under our U.S. DOE-supported program. Successful resolution of both  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine on an analytical scale has been achieved. The sample resolution in Appendix C shows that complete resolution of  $^{11}\text{C}$ -DL-tryptophan can be accomplished in 18 minutes at a flow rate of 3.0 ml/minute. A commercially available reverse phase HPLC column (Spherisorb ODS, 5  $\mu$ ) and a chiral mobile phase (0.017 M L-proline, 0.008 M cupric acetate in water) are used.

The method involves formation of a diastereoisomeric complex between cupric ions and the two amino acids, L-proline and the amino acid to be separated. In the case of resolution of DL-tryptophan, for example, the possible complexes are L-proline-Cu-D-tryptophan and L-proline-Cu-L-tryptophan, which are diastereoisomeric and can be separated by HPLC. The complex with tryptophan is more strongly bound by the HPLC support than the valine complex; therefore, a flow rate of 3.0 ml/minute is required to elute both tryptophan enantiomers in 17-18 minutes whereas 0.5 ml/minute will elute the valine enantiomers in the same time.

The eluent fraction containing the desired L-enantiomer can be collected using, in the case of  $^{11}\text{C}$ -labeled amino acids, a radioactivity monitor. This fraction still contains cupric acetate and L-proline, so a final purification step will be required prior to use. This can be accomplished by cation exchange chromatography and is simpler for  $^{11}\text{C}$ -L-tryptophan than for  $^{11}\text{C}$ -L-valine. For  $^{11}\text{C}$ -L-tryptophan, the acidified solution is simply loaded onto a cation exchange resin (AG 50W-X2, 50-100 mesh) and the resin assists in breaking up the complex with cupric acetate and L-proline. These components are washed through while the  $^{11}\text{C}$ -L-tryptophan is bound by the resin; after washing thoroughly with 1N HCl and with water, the amino acid is eluted with 0.2 N NaOH. The complex between  $^{11}\text{C}$ -L-valine, cupric acetate, and L-proline cannot be broken in this way. It is necessary to precipitate the copper using hydrogen sulfide, acidify, and filter to remove the cupric sulfide prior to loading onto the column. Excess hydrogen sulfide is easily removed by washing the column well with water prior to elution of the  $^{11}\text{C}$ -L-valine with 0.2 N NaOH, but  $^{11}\text{C}$ -L-valine apparently cannot be separated from L-proline by this method. This should not be a problem, however, since appreciable quantities of L-proline are found in the blood stream.

Scale-up of this procedure to a preparative HPLC column should produce  $^{11}\text{C}$ -L-tryptophan and  $^{11}\text{C}$ -L-valine in quantities sufficient for the proposed clinical studies. This should be completed by early in the first grant year. Tissue distribution studies using the  $^{11}\text{C}$ -labeled resolved amino acid to be studied clinically will be performed in two animal species in support of an Investigational New Drug (IND) application to be filed with the U. S. Food and Drug Administration; the agent will then be made available for clinical use by the start of the second grant year.

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Research Plan: Methods (continued)

Clinical Investigations

Clinical investigations using  $^{11}\text{C}$ -labeled amino acids in conjunction with positron emission computerized tomography will be divided into three phases over the 3-year study period.

During the first year emphasis will be placed on comparison of  $^{11}\text{C}$ -ACPC and  $^{11}\text{C}$ -ACBC and of  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine with regard to differential uptake in pancreas versus tumor in patients with strongly suspected pancreatic carcinoma. By the end of the first year our studies will be expanded beyond imaging into quantitative measurements of amino acid concentrations in pancreatic tumors before, during, and after treatment (see Quantitative Imaging). In the second year the  $^{11}\text{C}$ -labeled L-form of tryptophan or valine is expected to be available for clinical use. These clinical studies will then be completed in the third year.

Clinical investigations in the first year will first focus on comparing  $^{11}\text{C}$ -ACPC and  $^{11}\text{C}$ -ACBC using positron tomography in patients with suspected pancreatic carcinoma to determine whether  $^{11}\text{C}$ -ACPC might have an advantage over  $^{11}\text{C}$ -ACBC in the diagnosis of pancreatic tumors. Our previous experience with  $^{11}\text{C}$ -ACPC and rectilinear scanning (20) has shown that little  $^{11}\text{C}$ -ACPC is taken up by the human pancreas, but high concentrations of this unnatural amino acid have been observed in pancreatic tumors. On the other hand  $^{11}\text{C}$ -ACBC seems to concentrate almost as well in normal pancreas as in tumors of the pancreas.  $^{11}\text{C}$ -DL-Tryptophan and  $^{11}\text{C}$ -DL-valine will be similarly compared to further investigate the apparently greater pancreatic specificity of  $^{11}\text{C}$ -DL-tryptophan found in preliminary studies. In a separate study, we are planning to investigate the efficacy of  $^{11}\text{C}$ -labeled amino acids in conjunction with positron tomography for assessing the response of pancreatic carcinoma to therapy. This group of patients will be examined before, during, and after therapy with  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC and  $^{11}\text{C}$ -DL-tryptophan or  $^{11}\text{C}$ -DL-valine (depending on the results of the initial comparison of the two pairs of amino acids). The protocol for the first year is outlined in the following table (Table 2):

Table 2  
Clinical Investigations During First Year

No. Patients	Patient Selection Criteria*	Scanning Agent
8	Strongly suspected pancreatic Ca (pain, weight loss, steatorrhea and jaundice)	$^{11}\text{C}$ -ACPC and $^{11}\text{C}$ -ACBC on same day
8	As above	$^{11}\text{C}$ -DL-Tryptophan and $^{11}\text{C}$ -DL-valine on same day
10	Patients receiving chemotherapy and/or radiation therapy for pancreatic Ca**	$^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) and $^{11}\text{C}$ -DL-tryptophan (or $^{11}\text{C}$ -DL-valine) on same day x 3

\* The conventional diagnostic tests to support the suspicion or diagnosis of pancreatic disease are not expected to be paid for by this grant.

\*\* Positron tomography scans with the two preferred scanning agents will be done before, during, and after a course of therapy.

1079345

Continuation page

Research Plan: Methods (continued)

The endpoints of the first year's studies will be the following:

1. Decision on the superiority of  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC for selectively imaging pancreatic cancer with positron tomography.
2. Decision on the superiority of  $^{11}\text{C}$ -DL-tryptophan or  $^{11}\text{C}$ -DL-valine for imaging normal pancreatic tissue with positron tomography.
3. Collect scan data on 10 patients receiving treatment for pancreas carcinoma for quantitative analysis *by the end of the first year of funding period. We anticipate that we will have available an accurate quantitative ECAT II system for in vivo metabolic studies. Use of the updated ECAT system (ECAT II) should not only yield data amenable to quantification, but should also give us the advantage of simultaneous image reconstruction conjoint with image acquisition; this will allow for immediate rescanning, thus providing efficiency in instrument use.*
4. Determine correct diagnosis.
5. Determine morbidity and risk factors.

In the second year we will expand the series of quantitative in vivo studies by 5 patients in the pancreas cancer therapy group and also study patients with chronic pancreatitis during different phases of their disease. Each patient will be examined three times during the course of the disease as outlined in Table 3.

In addition, we project that  $^{11}\text{C}$ -L-tryptophan (or  $^{11}\text{C}$ -L-valine) will become available for clinical use by the start of second grant year. Therefore, 10 patients with suspected pancreatic carcinoma will be studied using  $^{11}\text{C}$ -L-tryptophan (or  $^{11}\text{C}$ -L-valine) in conjunction with  $^{11}\text{C}$ -ACPC (or  $^{11}\text{C}$ -ACBC) in a preliminary test of this regimen for differential diagnosis of pancreatic carcinoma.

Table 3

Clinical Investigations During Second Year

<u>No. Patients</u>	<u>Patient Selection Criteria</u>	<u>Scanning Agents</u>
5	Patients receiving chemotherapy and/or radiation therapy for pancreatic Ca*	$^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) and $^{11}\text{C}$ -DL-tryptophan (or $^{11}\text{C}$ -DL-valine) x 3
5	Patients with chronic pancreatitis*	$^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) and $^{11}\text{C}$ -DL-tryptophan (or $^{11}\text{C}$ -DL-valine) x 3
10	Patients with suspected pancreatic Ca**	$^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) and $^{11}\text{C}$ -L-tryptophan (or $^{11}\text{C}$ -L-valine)

\* Positron tomography scans will be done with the two preferred scanning agents at several stages of the disease.

\*\* Patients in whom the diagnosis of pancreatic carcinoma will be made might be entered into the treatment group if funds for cyclotron time are available.

1079346

Continuation page

Research Plan: Methods (continued)

Endpoints of the studies projected for the second year are to:

1. Determine the effect of successful treatment and tumor progression on the uptake of  $^{11}\text{C}$ -ACPC (or  $^{11}\text{C}$ -ACBC) and  $^{11}\text{C}$ -DL-tryptophan (or  $^{11}\text{C}$ -DL-valine) in patients undergoing therapy for pancreatic carcinoma.
2. Determine the effect of the phase of pancreatitis on the uptake of the same agents.
3. Determine whether ECAT II techniques can be applied to quantitate accurately amino acid extraction/utilization by tumors of the pancreas.
4. Determine whether the prognostic information obtained with this approach corresponds with the clinical response to therapy.

During the third year clinical studies with  $^{11}\text{C}$ -L-tryptophan (or  $^{11}\text{C}$ -L-valine) in conjunction with  $^{11}\text{C}$ -ACPC (or  $^{11}\text{C}$ -ACBC) to determine the potential of this method for the non-invasive, accurate diagnosis of pancreatic carcinoma will be completed. In addition the quantitative studies in patients undergoing treatment for pancreatic carcinoma will continue through the third year. The outline for the clinical studies during the third year is given in Table 4.

Table 4  
Clinical Investigations During Third Year

<u>No. Patients</u>	<u>Patient Selection Criteria</u>	<u>Scanning Agents</u>
10	Suspected pancreatic carcinoma*	$^{11}\text{C}$ -L-Tryptophan (or $^{11}\text{C}$ -L-valine) and $^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC)
10	Patients with proven pancreatic carcinoma undergoing chemotherapy**	$^{11}\text{C}$ -L-Tryptophan (or $^{11}\text{C}$ -L-valine) and $^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) x 3

\* Patients in whom the diagnosis of pancreatic carcinoma will be made might be entered into the treatment group if funds for cyclotron time are available.

\*\* Patients in this group will be scanned one time each before, during, and after the first course of cyclic chemotherapy.

Endpoints of clinical investigations in the third year will be to:

1. Verify in humans the potential utility of positron tomography using a combination of a natural  $^{11}\text{C}$ -labeled L-amino acid to visualize the normal pancreas and an unnatural  $^{11}\text{C}$ -labeled amino acid for the differential diagnosis of pancreatic disease.
2. To provide evidence that in vivo measurements of amino acid extraction/utilization by pancreatic cancer could be applied to accurately gauge the response of such cancers to therapy.
3. To collect information for a comparative cost analysis between conventional staging and gauging procedures used in developmental chemotherapy protocols and the in vivo measurements of the proliferative activity of pancreatic cancers as planned for this proposal.

1079347

Continuation page

Research Plan: Methods (continued)

Quantitative Imaging

It is well recognized that unwanted scattered radiation events occur as a function of scattering medium and count rate. True coincidence counting and the development of high quality images and accurate quantitation is the goal of positron tomography systems with their associated computational programs.

In our present system (ECAT I), singles, accidental coincidences, and scattered coincidence events tend to mask the true coincidence data. Extraneous events, accepted as true events, have accounted for up to 60% of the data collected in scans of phantoms using this system at *high count rates*.

In several of our phantom studies we have made attempts to linearize the response of our system to known concentration levels in the field of view. Computation techniques used have included background subtraction of data from the collected images and the development of software to estimate body densities and produce a refined body attenuation estimate for use in back projection algorithms.

Consistently, we have found that whatever technique we use, our correction scheme must take into account the total count rate of the system. For example with a low count rate phantom we found it best to back project using an 8% background subtract figure, but the same phantom required almost a 16% correction when the phantom count rate was four times as high.

The addition of a delayed coincidence gate and other associated hardware and software improvements available in the ECAT II system will allow us to estimate the amount of "random" coincidences occurring in the image as it is collected and permit real time or later "randoms" correction. While this technique will not remove all unwanted events, it will tend to linearize the system with respect to its present intensity versus count rate nonlinearities. At this point, our image correction routines could be more appropriately, and presumably universally, applied.

We shall specifically therefore continue software development which will yield improved images, by acquiring experience with both patient and phantom studies, and applying and upgrading our analysis schemes. Our present schemes, as mentioned, include operations such as background subtract, outlier squelching, normalization, transmission data file manipulation, etc. It is anticipated that some combination of these methods, including perhaps an as yet untried Compton scattering correction routine, will yield a computational protocol which will be invariant from phantom to phantom, count rate independent, and linear (35,36).

Listed below are some of the computation techniques we will study:

## 1. Emission Data Corrections:

## a. Background subtraction techniques

- (1) Constant value
- (2) Percentage of maximum
- (3) Ramp(s) calculated from data files to edge of body
- (4) Combinations of 1,2,3
- (5) Nonlinear amount based upon square of count rate

## b. Blanking outside body outline

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Continuation page

Research Plan: Methods (continued)

2. Transmission Data Corrections
  - a. Single level transmission data estimation
  - b. Multilevel body outline estimation
  - c. Data bounding, smoothing
3. Transmission-corrected Emission Data
  - a. Data bounding (outlier squelching)
  - b. Data projection normalization
  - c. Randoms subtraction (linear and nonlinear)

Our approach to quantification will include detailed studies of the effects of scattered radiation on the quality of our collected data. For example, a typical human torso, if modeled as an ellipse, might be 15 cm along the short axis and 30 cm along the long axis. A point source, located at the origin of this ellipse, would not be equally sensed in all projections, due to varying thicknesses of material between the source and sensor. In fact, using an attenuation coefficient of  $0.1 \text{ cm}^{-1}$ , only 7.4 to 22.5% of the radiation would be sensed in any given projection, compared to the non-attenuated case.

At 511 keV, for water, only 35% of incident gamma rays are absorbed in Compton scattering, the remainder are primarily forward scattered albeit at a degraded energy level. It is apparent from our phantom studies that some of this forward scattered radiation must be being detected, as calculations on both emission and transmission data show increases in count rate levels over that predicted by theory for phantoms with attenuation. This data has been confirmed both by comparing sensed radiation levels for various phantoms involving several levels of activity, and by comparing transmission data through known thicknesses of water with that of air. Further, from observation of all phantom and patient data, we note that radiation is sensed in all areas of the initial data files where there is only air present.

Preliminary data has indicated to us that the Compton scattering phenomena, at least as measured in air outside our phantoms, might be mathematically modeled as arising from a convolution of an exponential function with an apparent true distribution. The rate of fall of the exponential function seems somehow to be related to the attenuation properties of the phantom. An explanation for this behavior will be one of our goals.

E. Human Subjects

1. It is anticipated that approximately 30 patients with proven cancer of the pancreas, and 35 patients with strongly suspected cancer of the pancreas will be studied during a 3-year period. Pregnant women and patients under 18 years of age will not be included in the study. Racial or ethnic background of the patients is no selection criterion, and only patients capable of giving informed consent will be accepted to participate in the clinical investigations outlined in this proposal.

2. Recruitment and initial consent of prospective patients will be respectively obtained by referring physicians who are collaborators in the project or local physicians who are familiar with the project. After the initial discussion with their primary physician, the patients will be informed about the pro-

Research Plan: Human Subjects (continued)

cedures and tests about 1 to 2 hours prior to the examination. The consent forms to be used are approved by the ORAU/ORNL Committee on Human Studies, consent will be usually obtained by a physician involved in the project. The purpose of the procedure, the chemical aspects with regard to the amino acids and the radiological aspects with regard to the  $^{11}\text{C}$ -label of the radiopharmaceuticals as well as the scanning procedure will always be discussed with the patient. The discussion takes place usually in the presence of a nurse, and the patient is encouraged to ask questions and reminded that he can withdraw from the study at any time. The signed consent forms are to be kept in the patient's record.

3. There are no physical risks other than the radiation dose (compatible with extensive diagnostic radiographic procedures); there are no psychological, social or legal risks. There are no alternative methods for the in vivo metabolic studies proposed in this application.

4. The activity level ( $^{11}\text{C}$ ) of the amino acid dose is to be kept at 14 mCi which is less than 30% of the dose approved by the FDA for a 70 kg person.

5. Potential benefits include information on the extent of the disease and possible useful metabolic information on tumor growth for therapeutic decisions.

6. The risk as related to potential benefits is minimal.

F. Laboratory Animals

None involved.

G. Consultants

Dr. Paul King of the Department of Biomedical Engineering, Vanderbilt University, Nashville, Tennessee, will be a consultant to the project. Dr. King has a high level of expertise in the area of software development for improved computer applications with the ECAT positron tomographic scanner.

Drs. I. R. Collmann of the University of Tennessee Memorial Research Center and Hospital, Knoxville, Tennessee, and G. Avant, Vanderbilt University Hospital, Nashville, Tennessee, are gastroenterologists who will refer patients for the proposed studies and consult with the principal investigator on the clinical protocols to be followed and the interpretation of the clinical data.

Mr. A. P. Callahan of the Nuclear Medicine Technology Group, Oak Ridge National Laboratory, will be involved in hot cell operation and general consultation in the area of radioactive syntheses (at no cost to the project). The 86-inch cyclotron and associated hot cell facilities are to be made available for production of the  $^{11}\text{C}$ -labeled amino acids which will be used in the proposed studies.

H. Consortium ArrangementsUse of Department of Energy (DOE) Facilities and DOE Contract Requirements

This research grant application includes a segment of activity which would be performed in facilities of DOE and governed by an existing contract between Oak

1079350

Continuation page

Research Plan: Consortium Arrangements (continued)

Ridge Associated Universities (ORAU) and the DOE. The DOE has reviewed this proposal and has concurred in ORAU conducting the described work in the DOE facilities made available for biomedical research, subject to payment to the DOE by ORAU from NIH funds of the applicable direct and indirect cost of the work (not including any charge for the use of DOE facilities) as determined by the provisions of DOE's contract with ORAU.

It is believed that in large measure the requirements of the DOE contract parallel conditions which NIH ordinarily applies to its grants. In the event of differences between NIH grant terms and the DOE 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 DOE for direct resolution with NIH.

By way of general information, ORAU's contract with the DOE is a cost-type contract financed under a Government-fund account. The specific contract work is formulated in cooperation with the DOE and authorized within general guidelines in the contract. Contract terms include DOE responsibilities for Government ownership and control of inventions, data, and other research products. Ownership of all equipment and facilities acquired by ORAU with DOE 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.

Collaborative Arrangements

The radiopharmaceutical development/nuclear medicine programs of the Oak Ridge Associated Universities Medical and Health Sciences Division have a long-standing collaborative arrangement with Oak Ridge National Laboratory, particularly the Nuclear Medicine Technology Group (Health and Safety Research Division) and the staff associated with the 86-inch cyclotron (Operations Division). These collaborative ties date back to joint participation in a grant proposal entitled "ORAU/ORNL Study of Carbon-11 in Nuclear Medicine," which was funded by NCI in 1974; continued collaboration will be very important in the proposed project. The principal investigator and the applicant organization are prepared to establish in writing the required inter-institutional agreements.

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## Research Plan: Literature cited (continued)

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CHECKLIST

This is the required last page of the application.

Check the appropriate boxes and provide the information requested.

TYPE OF APPLICATION:

- NEW application (This application is being submitted to the PHS for the first time.)
- COMPETING CONTINUATION of grant number: \_\_\_\_\_  
(This application is to extend a grant beyond its original project period.)
- SUPPLEMENT to grant number: \_\_\_\_\_  
(This application is for additional funds during a funded project period.)
- REVISION of application number: CA 29490-01  
(This application replaces a prior version of a new, competing continuation or supplemental application.)
- Change of Principal Investigator/Program Director.  
Name of former Principal Investigator/Program Director: \_\_\_\_\_

ASSURANCES IN CONNECTION WITH:

Civil Rights	Handicapped Individuals	Sex Discrimination	Human Subjects General Assurance (if applicable)	Laboratory Animals (if applicable)
<input checked="" type="checkbox"/> Filed <input type="checkbox"/> Not filed				

INDIRECT COSTS:

Indicate the applicant organization's most recent indirect cost rate established with the appropriate DHEW Regional Office. If the applicant organization is in the process of initially developing or renegotiating a rate, or has established a rate with another Federal agency, it should, immediately upon notification that an award will be made, develop a tentative indirect cost rate proposal based on its most recently completed fiscal year in accordance with the principles set forth in the pertinent DHEW Guide for Establishing Indirect Cost Rates, and submit it to the appropriate DHEW Regional Office. Indirect costs will not be paid on foreign grants, construction grants, and grants to individuals, and usually not on grants in support of conferences.

DHEW Agreement Dated: 12-19-79  
 \_\_\_\_\_ % Salary and Wages or 52.83 % Total Direct Costs.

Is this an off-site or other special rate, or is more than one rate involved?  YES  NO

Explanation: \_\_\_\_\_

- DHEW Agreement being negotiated with \_\_\_\_\_ Regional Office.
- No DHEW Agreement, but rate established with \_\_\_\_\_ Date \_\_\_\_\_
- No Indirect Costs Requested.

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NAME (last, first, middle initial)

bnier, Karl F.

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Continuation page

APPENDIX

- A. Reprint of reference 16 (Washburn, L.C., Sun, T.T., Byrd, B.L., et al. High-level production of C-11-carboxyl-labeled amino acids. In Radiopharmaceuticals II, Proceedings of 2nd International Symposium on Radiopharmaceuticals, Seattle, Wash., 1979, pp. 767-777).
- B. Examples of positron tomographic scans obtained with <sup>11</sup>C-labeled amino acids.
- C. Example of analytical-scale resolution of <sup>11</sup>C-DL-tryptophan using high pressure liquid chromatography.

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U.S. DEPARTMENT OF ENERGY  
**memorandum**

DATE APR 15 1980

REPLY TO EV-30  
ATTN OF

SUBJECT ORAU "Work For Others" Research Proposals

TO K. M. Haythorn, Director  
Energy Programs and Support Division, OR

The OHER has reviewed the following ORAU "Work For Others" research proposals, and we have determined that the proposed work is of direct programmatic benefit to DOE. In confirmation of my staff's verbal approval to Robin L. Spradlen on 3/10/80, we approve their submission to the appropriate sponsors for funding consideration:

1. "Nutrition and Resistance of Lung Cells to Oxidants," grant application 20-80-80, Richard M. Arneson, principal investigator. [Sponsor: NIH, 3 years for \$264,600 total direct costs with \$97,700 first year (12/1/80 - 11/30/81), \$80,700 second year, and \$86,200 third year. P. L. Johnson, ORAU, letter of 2/5/80 to K. M. Haythorn, OR. K. M. Haythorn, OR, memorandum of 2/12/80 to W. W. Burr, EV-30, recommended approval at fund cost.]
2. "C-11-Amino Acids/Positron ECT for Pancreatic Studies," grant application 20-81-80, Karl F. Hubner, principal investigator. [Sponsor: NIH, 3 years for \$475,425 total direct costs with \$225,675 first year (12/1/80 - 11/30/81), \$127,250 second year, and \$122,500 third year. P. L. Johnson, ORAU, letter of 2/15/80 to K. M. Haythorn, OR. K. M. Haythorn, OR, memorandum of 2/25/80 to W. W. Burr, EV-30, recommended approval at fund cost.]

*W. W. Burr, Jr.*  
 W. W. Burr, Jr., M.D., Director  
 Office of Health and Environmental  
 Research, Office of Environment

Oak Ridge  
Associated  
Universities

March 24, 1980

Mr. Kenneth M. Haythorn, Director  
Energy Programs and Support Division  
Department of Energy  
Oak Ridge, Tennessee 37830

Subject: GRANT APPLICATION ENTITLED *C-11-AMINO ACIDS/POSITRON ECT FOR  
PANCREATIC STUDIES*

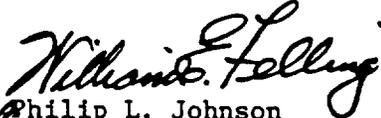
Dear Mr. Haythorn:

Enclosed are three copies of a grant application for a new project entitled *C-11-Amino Acids/Positron ECT for Pancreatic Studies*. Draft copies of this proposal were forwarded to your office for review on February 15, 1980 and approval for transmittal was given by Dr. Benson on March 24.

The proposed research will be carried out under policies and procedures previously established between ORAU and DOE and will be supervised by Dr. Karl Hübner.

We will keep you advised concerning the status of this grant.

Sincerely,

  
Philip L. Johnson  
Executive Director

RYAN:br

Enclosures

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Oak Ridge  
Associated  
Universities

Post Office Box 117  
Oak Ridge, Tennessee 37830  
Telephone 615 576-3300

Executive  
Office

March 24, 1980

Isidore Cohn, Jr., M.D.  
National Pancreatic Cancer Project  
L.S.U. Medical Center  
1542 Tulane Avenue  
New Orleans, Louisiana 70112

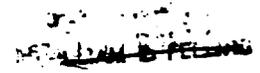
Dear Dr. Cohn:

Enclosed are twenty copies of a grant application entitled *C-11 Amino-Acids/Positron ECT for Pancreatic Studies*. This project will be supervised by Dr. Karl F. Hübner.

Oak Ridge Associated Universities is a nonprofit corporation sponsored by 50 Southern colleges and universities. The major portion of its activities are carried out under a long-term operating contract with the U. S. Department of Energy. Certain conditions arising from this relationship between ORAU and the DOE are set forth under Section E of this application.

If questions should arise during the review of this proposal, please do not hesitate to call Dr. Hübner at area code 615, 576-3098.

Sincerely,

  
Philip L. Johnson  
Executive Director

br

Enclosures

bcc: Mr. Kenneth M. Haythorn DOE ORO (3) ←  
Executive Office (2)  
K. F. Hübner  
J. T. Crockett

1079358

SECTION I

DEPARTMENT OF  
HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE

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GRANT APPLICATION

TYPE	PROGRAM	NUMBER
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)  
C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES

2. PRINCIPAL INVESTIGATOR

2A. NAME (Last, First, Initial)  
Hübner, Karl F.

2B. TITLE OF POSITION  
Chief Clinician, Medical and Health Sciences Division

2C. MAILING ADDRESS (Street, City, State, Zip Code)  
Oak Ridge Associated Universities  
P. O. Box 117  
Oak Ridge, Tennessee 37830

2D. DEGREE  
M.D.

2E. SOCIAL SECURITY NO.  
[REDACTED]

2F. TELEPHONE DATA  
Area Code: 615  
TELEPHONE NUMBER AND EXTENSION: 576-3098

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

2H. MAJOR SUBDIVISION (See Instructions)  
Medical and Health Sciences Division

3. DATES OF ENTIRE PROPOSED PROJECT PERIOD (This application)  
FROM: 12/1/80 THROUGH: 11/30/83

4. TOTAL DIRECT COSTS REQUESTED FOR PERIOD IN ITEM 3  
\$475,425

5. DIRECT COSTS REQUESTED FOR FIRST 12-MONTH PERIOD  
\$225,675

6. PERFORMANCE SITE(S) (See Instructions)  
Medical and Health Sciences Division  
Oak Ridge Associated Universities  
P. O. Box 117  
Oak Ridge, Tennessee 37830

7. Research Involving Human Subjects (See Instructions)  
A.  NO B.  YES Approved: \_\_\_\_\_ Date \_\_\_\_\_  
C.  YES - Pending Review

8. Inventions (Renewal Applicants Only - See Instructions)  
A.  NO B.  YES - Not previously reported  
C.  YES - Previously reported

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  
IRS No. 62-0476816  
Congressional District No. 3

10. NAME, TITLE, AND TELEPHONE NUMBER OF OFFICIAL(S) SIGNING FOR APPLICANT ORGANIZATION(S)  
Dr. Philip L. Johnson  
Executive Director  
Oak Ridge Associated Universities  
P.O. Box 117  
Oak Ridge, TN.  
Telephone Number (s) (615) 576-3300

11. TYPE OF ORGANIZATION (Check applicable item)  
 FEDERAL  STATE  LOCAL  OTHER (Specify)  
Private Corporation, Non-Profit

12. NAME, TITLE, ADDRESS, AND TELEPHONE NUMBER OF OFFICIAL IN BUSINESS OFFICE WHO SHOULD ALSO BE NOTIFIED IF AN AWARD IS MADE  
W. F. Countiss  
Head, Office of Fiscal Services  
Oak Ridge Associated Universities  
P. O. Box 117  
Oak Ridge, TN. 37830  
Telephone Number (615) 576-3056

13. IDENTIFY ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT PURPOSES (See Instructions)  
Other (Medical and Health Sciences Division)

14. ENTITY NUMBER (Formerly PHC Account Number)  
1620476816A

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 <i>Philip L. Johnson</i>	DATE 9-25-80

## SECTION 1

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE

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PROJECT NUMBER

## RESEARCH OBJECTIVES

## 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

Karl F. Hübner, [REDACTED] Chief Clinician, Nuclear Medicine; Lee C. Washburn, [REDACTED] Scientist, Radiochemistry; Raymond L. Hayes, [REDACTED] Chief Scientist, Radiochemistry; Paul H. King, [REDACTED] Associate Prof., Biomedical Engineer; G. A. Digenis, [REDACTED] Consultant, Radiopharmacy; I. R. Collmann, [REDACTED] Prof. Medicine, Gastroenterology; S. Krauss, [REDACTED] Director, Hematology-Oncology.

## TITLE OF PROJECT

## C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES

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

Cancer of the pancreas is one of the leading causes of death among cancer patients. This can be attributed in part to the fact that a definitive diagnosis is usually made only at an advanced stage of the disease. We have shown, using positron emission computerized tomography (positron ECT) that <sup>11</sup>C-labeled DL-tryptophan and valine show high preferential uptakes in normal pancreatic tissue and that their uptake in pancreatitis is highly depressed. Since the L-isomers of these two amino acids have an affinity for normal pancreas while the D-isomers tend to be preferentially taken up by tumor tissue, approximately the same <sup>11</sup>C-concentrations are observed in both normal and malignant pancreatic tissues when the DL mixture is administered. We propose to develop rapid methods for the separation of the L-isomers of tryptophan and valine from their <sup>11</sup>C-labeled racemates. Using these purified agents pancreatic cancer would then be observed as zones of decreased or absent <sup>11</sup>C pancreatic deposition in the three-dimensional cross-sectional images obtained with positron ECT. Confirmation of the presence of a malignant lesion(s) could then be made with <sup>11</sup>C-labeled 1-aminocyclopentanecarboxylic acid or its cyclobutane analog, radiopharmaceuticals which we have shown to be effective tumor-localizing agents having low affinities for inflammatory lesions. This diagnostic protocol should thus provide a non-invasive method for the complete differential diagnosis of pancreatic disease. We also propose to use positron ECT to make quantitative measurements of the effect of therapy on the extraction/utilization of amino acids by pancreatic neoplasms as a possible method of metabolically gauging individual tumor responses to treatment.

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

DESCRIPTION	1ST PERIOD (SAME AS DE TAILED BUDGET)	ADDITIONAL YEARS SUPPORT REQUESTED (This application only)					
		2ND YEAR	3RD YEAR	4TH YEAR	5TH YEAR	6TH YEAR	7TH YEAR
PERSONNEL COSTS	61,125	65,250	69,800				
CONSULTANT COSTS (Include fees, travel, etc.)	3,600	7,200	3,600				
EQUIPMENT	121,000	0	0				
SUPPLIES	4,150	4,800	4,500				
TRAVEL	DOMESTIC	2,300	3,700	2,600			
	FOREIGN						
PATIENT COSTS	1,500	3,300	2,800				
ALTERATIONS AND RENOVATIONS							
OTHER EXPENSES	32,000	43,000	39,200				
<b>TOTAL DIRECT COSTS</b>	<b>225,675</b>	<b>127,250</b>	<b>122,500</b>				

**TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Enter on Page 1, Item 4) → \$ 475,425**

**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.)

Recurring increases in personnel costs computed at 7% average.

2nd Year Cost Increase Justification: Increases in consultant costs, patient transportation costs and other costs (primarily cyclotron usage) for the second year are a result of increasing the number of patients studied. Some patients will be studied during the first year, but a large portion of the year will be spent upgrading the ECAT and related pharmacological systems. The second year will involve larger numbers of patients thus increasing funds spent for Dr. Paul King, transportation of patients and additional cyclotron runs.

Equipment Justification

Our experience with the ORTEC ECAT I scanning system using phantoms has indicated to us that this system, while producing images of diagnostic quality, does not yield data which are amenable to quantitation. We propose, therefore, to upgrade our instrument to an ECAT II system so that a major contributing factor, accidental coincidences ("randoms") may be eliminated. Another major advantage of the ECAT II system is the fact that simultaneous image reconstruction conjoint with image acquisition can be made; this will permit scanning to proceed while reconstruction of the previous scan is in process, thus greatly improving the efficiency of the system. When the present ECAT I is upgraded to an ECAT II version, this equipment will have

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NA	(last, first, middle initial)
Hubner, Karl F.	
SOCIAL SECURITY NUMBER	
[REDACTED]	

Continuation page

\* Hard and Soft-ware to update ECAT I to ECAT II

We have requested DOE funds to purchase the hard and soft-ware required to update our ECAT I scanner. Should DOE approve and fund our request, the total requested for the 1st year and entire project period of this grant proposal would be reduced by \$121,000.

DO NOT TYPE IN THIS SPACE BINDING MARGIN

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**BIOGRAPHICAL SKETCH**

Provide 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.

<b>NAME</b> Karl F. Hübner	<b>TITLE</b> Director, Outpatient Nuclear Medicine	<b>BIRTHDATE (Mo., Day, Yr.)</b> [REDACTED]
<b>PLACE OF BIRTH (City, State, Country)</b> [REDACTED] Germany	<b>PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)</b> USA	<b>SEX</b> <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female

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

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

**HONORS**

[REDACTED]

<b>MAJOR RESEARCH INTEREST</b> Nuclear Medicine; Oncology; Radiation Biology and Medicine	<b>ROLE IN PROPOSED PROJECT</b> Principal Investigator - Clinician
---	---

**RESEARCH SUPPORT (See instructions)**

Total salary and research support is through Department of Energy Contract Number DE-AC05-76OR00033; "Radiation Emergency Assistance Center/Training Site, \$934,000; Coal-Related Disease Detection, \$103,000; Clinical Development of Radiopharmaceuticals, \$210,000."

**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.)**

- 1977 - Present Director, Radiation Emergency Assistance Center/Training Site, Oak Ridge Associated Universities, Oak Ridge, TN.
- 1975 - Present Director, Outpatient Nuclear Medicine, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.
- 1973 - 1974 Senior Research Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.
- 1971 - 10/73 Senior Staff Member with Clinical Staff, Medical Division, Oak Ridge Associated Universities, Oak Ridge, TN.
- 1967 - 1970 Research Associate in Experimental Immunology, Medical Division, Oak Ridge Associated Universities, Oak Ridge, TN.
- 1964 - 1967 Resident in Pediatrics, University of Tübingen, Medical School, Germany
- 1962 - 1964 Resident in Clinical Investigation, Medical Division, Oak Ridge Institute of Nuclear Studies (now Oak Ridge Associated Universities), Oak Ridge, TN.
- 1960 - 1961 Internship (rotating) at 2nd General Hospital of the U.S. Army, and at the 86th Tactical Hospital of the U.S. Air Force, Germany.

1079364

Continuation page

## Publications: (Karl F. Hübner)

Partain, C.L., Hübner, K.F., Stabb, E.V., Scatliff, J.H., Miller, G.F., and Gibbs, W.D. CSF kinetics: comparison of nuclear medicine, contrast enhanced CT, and positron emission tomography. *Investigative Radiology* 14(5):377, Sept.-Oct., 1979 (abstract).

Buonocore, E., and Hübner, K.F. Comparison of positron emission computer assisted transaxial tomography (ECT) with transmission CT and ultrasonography for the diagnosis of pancreatic disease. Presented at the Eastern Radiological Society, Mid Pines, North Carolina, April, 1979 (abstract).

Hübner, K.F., Buonocore, E., Gibbs, W.D., Holloway, S., and Byrd, B.L. Differentiation of pancreatic and other retroperitoneal tumors by positron emission computerized tomography (ECT). *J. Nucl. Med.* 20:631, 1979. (abstr.)

Hübner, K.F., Andrews, G.A., Washburn, L., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Winebrenner, J.D. Tumor location with 1-aminocyclopentane[<sup>11</sup>C]-carboxylic acid: preliminary clinical trials with single-photon detection. In *Year Book of Cancer*, R.L. Clark, R.W. Cumley and R.C. Hickey, eds., Year Book Medical Publishers, Inc., Chicago, 1979, pp. 237-239.

Hübner, K.F., and Buonocore, E. Emission computerized tomography (ECT) with <sup>11</sup>C-labeled amino acids, transmission CT and ultrasonography (US) in the diagnosis of pancreatic disease. Presented at the Sixth International Congress of Radiation Research, Tokyo, Japan, 1979 (abstract).

Hübner, K.F., Andrews, G.A., Buonocore, E., Hayes, R.L., Washburn, L.C., Collmann, I.R. and Gibbs, W.D. Carbon-11-labeled amino acids for the rectilinear and positron tomographic imaging of the human pancreas. *J. Nucl. Med.* 20:507-513, 1979.

Buonocore, E., Hübner, K.F., and Collmann, I.R. Differentiation of retroperitoneal tumor using positron emission computed tomography. *J. Comput. Asst. Tomogr.* 3(6): 825-828, 1979.

Buonocore, E., and Hübner, K.F. Positron-emission computed tomography of the pancreas: a preliminary study. *Radiology* 133:195-201, 1979.

Buonocore, E., and Hübner, K.F. Comparison of positron emission computer assisted transaxial tomography (ECT) with transmission CT and ultrasonography for the diagnosis of pancreatic disease. Presented at the Annual meeting of the Radiological Society of North America, Chicago, Illinois, 1978 (abstract).

Sauerbrunn, B.J.L., Andrews, G.A., and Hübner, K.F. <sup>67</sup>Ga-citrate imaging in genitourinary tract tumors: report of cooperative study. *J. Nucl. Med.* 19:470-475, 1978.

Lushbaugh, C.C., Hübner, K.F., and Ricks, R.C. Medical aspects of nuclear radiation emergencies. *Emergency* 10:32-35, 1978.

Lawless, D., Brown, D.H., Hübner, K.F., Colyer, S.P., Carlton, J.E., and Hayes, R.L. Isolation and partial characterization of a <sup>67</sup>Ga-binding glycoprotein from Morris 5123C rat hepatoma. *Can. Res.* 38:4440-4444, 1978.

Hübner, K.F., Hayes, R.L., Washburn, L.C., Gibbs, W.D., Byrd, B.L., and Butler, T.A. Scanning of the human pancreas with DL-valine-1-<sup>11</sup>C and DL-tryptophan-1-<sup>11</sup>C. *J. Nucl. Med.* 19:686, 1978 (abstract).

NAME (last, first, middle initial)

Hübner, Karl F.

SOCIAL SECURITY NUMBER

Continuation page

Publications: (Karl F. Hübner, continued)

Hübner, K.F., Andrews, G.A., Gibbs, W.D., Holloway, S., Hayes, R.L., and Washburn, L.C. Initial diagnostic results with  $^{11}\text{C}$ -labeled amino acids and the emission positron tomograph. In Proceedings of the Second World Federation of Nuclear Medicine and Biology, p. 13 (abstract), Washington, D.C., 1978.

Andrews, G.A., Hübner, K.F., and Greenlaw, R.H. Gallium-67 citrate imaging in malignant lymphoma: final report of cooperative group. J. Nucl. Med. 19:1013-19, 1978.

Johnston, G.S., Go, M.F., Benua, R.S., Larson, S.M., Andrews, G.A., and Hübner, K.F.  $^{67}\text{Ga}$ -citrate imaging in Hodgkin's disease: final report of cooperative group. J. Nucl. Med. 18:692-698, 1977.

Hübner, K.F., Andrews, G.A., Washburn, L., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Winebrenner, J.D. Tumor location with 1-aminocyclopentane[ $^{11}\text{C}$ ]-carboxylic acid: preliminary clinical trials with single-photon detection. J. Nucl. Med. 18:1215-1221, 1977.

Hübner, K.F., Andrews, G.A., Lushbaugh, C.C., and Tompkins, E. A follow-up study program for persons irradiated in radiation accidents. In Handling of Radiation Accidents 1977, Proceedings of a Symposium, pp. 57-70. Vienna, Austria: International Atomic Energy Agency, 1977.

Hübner, K.F., Andrews, G.A., Hayes, R.L., Poggenburg, J.K., and Solomon, A. The use of rare earth radionuclides and other bone-seekers in evaluating bone lesions in patients with multiple myeloma and solitary plasmacytoma. Radiology 125:171-176, October, 1977.

Andrews, G.A., Hübner, K.F., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Collmann, I.R. Clinical studies of  $^{11}\text{C}$ -labeled amino acids. J. Nucl. Med. 18:638, 1977 (Poster Session, abstract).

Andrews, G.A., Hübner, K.F., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., and Butler, T.A. Clinical tumor scanning with  $^{11}\text{C}$ -carboxyl-labeled 1-aminocyclopentanecarboxylic acid ( $^{11}\text{C}$ -ACPC). Presented at the 17th Annual Southeastern Chapter of the Society of Nuclear Medicine, Louisville, Kentucky, 1976 (abstract).

Hübner, K.F. and Littlefield, L.G. Burkitt's lymphoma in three American children. Clinical and cytogenetic observations. Am. J. Dis. Child. 129:1219-1223, Oct., 1975.

Swartzendruber, D.C. and Hübner, K.F. Effect of external whole-body X-irradiation on gallium-67 retention in mouse tissues. Radiat. Res. 55:457-468, 1973.

Gengozian, N., Edwards, C.L., Vodopick, H.A., and Hübner, K.F. Bone marrow transplantation in a leukemic patient following immunosuppression with antithymocyte globulin and total body irradiation. Transplantation 15:446-454, 1973.

Gengozian, N. and Hübner, K.F. "In situ" visualization of a graft-vs-host reaction. J. Immunol. 106:1159-1165, 1971.

Hübner, K. and Brown, D.W. Scanning of the spinal subarachnoid space after intrathecal injection of  $^{131}\text{I}$  labeled human serum albumin. J. Nucl. Med. 6:465-472, 1965.

1079366

SECTION II - PRIVILEGED COMMUNICATION

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 Lee C. Washburn		TITLE Scientist		BIRTHDATE (Mo., Day, Yr.) [REDACTED]	
PLACE OF BIRTH (City, State, Country)		PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date) USA		SEX <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female	
EDUCATION (Begin with baccalaureate training and include postdoctoral)					
INSTITUTION AND LOCATION		DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD	
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]	
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]	
HONORS [REDACTED]					
MAJOR RESEARCH INTEREST Radiopharmaceutical development			ROLE IN PROPOSED PROJECT Resolution of <sup>11</sup> C-labeled amino acids and production of these agents for clinical use.		

RESEARCH SUPPORT (See instructions)

Total salary and research support through Department of Energy Contract Number DE-AC05-76OR00033.

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.)

April 1974 - present      Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.  
 June 1972 - March 1974    Presidential Intern, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.  
 March-June 1972          Research Associate, Vanderbilt University, Nashville, TN.

Publications:

Jay, M., Digenis, G.A., Chaney, J.E., Washburn, L.C., Byrd, B.L., Hayes, R.L., and Callahan, A.P. Synthesis and brain uptake of carbon-11 phenethylamine. (Submitted for publication)

Blank, M.L., Cress, E.A., Byrd, B.L., Washburn, L.C., and Snyder, F. Liposomal encapsulated Zn-DTPA for removing intracellular heavy metals. (Submitted for publication)

Digenis, G.A., Casey, D.L., Wesner, D.A., Washburn, L.C., and Hayes, R.L. Preparation of optically active C-11-amino acids. J. Nucl. Med. 20:662, 1979 (abstract).

Hubner, K.F., Andrews, G.A., Buonocore, E., Hayes, R.L., Washburn, L.C., Collmann, I.R. and Gibbs, Wm. D. Carbon-11-labeled amino acids for the rectilinear and positron tomographic imaging of the human pancreas. J. Nucl. Med. 20:507-513, 1979.

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Continuation page

Publications: (Lee C. Washburn)

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. [Carboxyl-<sup>11</sup>C] l-Aminocyclobutanecarboxylic acid, a potential agent for tumor localization. J. Nucl. Med. 20:1055-1061, 1979.

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. DL-[Carboxyl-<sup>11</sup>C] tryptophan, a potential agent for pancreatic imaging: production and preclinical investigations. J. Nucl. Med. 20:857-864, 1979.

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., Butler, T.A., and Callahan, A.P. High-Level production of C-11-carboxyl-labeled amino acids. In Radiopharmaceuticals II, proceedings of 2nd International Symposium on Radiopharmaceuticals, Seattle, Wash., 1979, pp. 767-777.

Lushbaugh, C.C. and Washburn, L.C. FDA IND Approval for Zn-DTPA, new clinical agent for decorporation therapy of actinides. J. Nucl. Med. 20:73, 1979.

Lushbaugh, C.C. and Washburn, L.C. FDA IND Approval for Zn-DTPA, new clinical agent for decorporation therapy of actinides. Health Phys. 36:472, 1979.

Lushbaugh, C.C. and Washburn, L.C. Decorporation therapy of actinides. Health Physics Newsletter 6:5, 1978.

Lushbaugh, C.C. and Washburn, L.C. FDA IND Approval for Zn-DTPA, new clinical agent for decorporation therapy of actinides. J. Occupational Med. 20:720, 1978.

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. Further pre-clinical studies of C-11-DL-tryptophan, a potential pancreas-imaging agent. In Proc. of the 2nd International Congress of the World Federation of Nuclear Medicine and Biology, Washington, D.C., September 17-21, 1978, p. 41.

Hayes, R.L., Washburn, L.C., Wieland, B.W., Sun, T.T., Turtle, R.R., and Butler, T.A. Carboxyl-labeled <sup>11</sup>C-l-aminocyclopentanecarboxylic acid, a potential agent for cancer detection. Year Book of Cancer 1978, pp. 236-237.

Washburn, L.C., Sun, T.T., Anon, J.B., and Hayes, R.L. Effect of structure on tumor specificity of alicyclic  $\alpha$ -amino acids. Cancer Res. 38:2271-2273, 1978.

Washburn, L.C., Wieland, B.W., Sun, T.T., Hayes, R.L., and Butler, T.A. [l-<sup>11</sup>C] DL-Valine, a potential pancreas-imaging agent. J. Nucl. Med. 19:77-83, 1978.

Hayes, R.L., Washburn, L.C., Wieland, B.W., Sun, T.T., Butler, T.A., and Callahan, A.P. Synthesis and purification of <sup>11</sup>C-carboxyl-labeled amino acids. J. Appl. Radiat. Isotopes 29:186-187, 1978.

Washburn, L.C. and Hayes, R.L. Importance of excess base in the synthesis of sodium phosphorothioate. In Inorganic Syntheses, Vol. 17, A. G. MacDiarmid, ed., McGraw-Hill Book Co., 1978, pp. 193-194.

Washburn, L.C., Sun, T.T., Anon, J.B., and Hayes, R.L. Effect of structural modifications on the tumor specificity of alicyclic  $\alpha$ -amino acids. In Proc. of the 18th Annual Meeting of the Southeastern Chapter, Society of Nuclear Medicine, Part 2, Winston-Salem, N.C., October 12-15, 1977 (abstract).

Continuation page

Publications: (Lee C. Washburn)

Hubner, K.F., Andrews, G.A., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Winebrenner, J.D. Tumor location with 1-aminocyclopentane [ $^{11}\text{C}$ ] carboxylic acid: preliminary clinical trials with single-photon detection. *J. Nucl. Med.* 18:1215-1221, 1977.

Andrews, G.A., Hubner, K.F., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Collmann, I.R. Clinical studies of C-11-labeled amino acids. *J. Nucl. Med.* 18:638, 1977 (abstract).

Washburn, L.C., Sun, T.T., Wieland, B.W., and Hayes, R.L. C-11-DL-Tryptophan, a potential pancreas-imaging agent for positron tomography. *J. Nucl. Med.* 18:638, 1977 (abstract).

Hayes, R.L., Washburn, L.C., Wieland, B.W., and Sun, T.T. Carboxyl-labeled C-11-ACBC, a possible new radiopharmaceutical for detection of cancer using positron tomography. *J. Nucl. Med.* 18:639, 1977 (abstract).

Washburn, L.C., Wieland, B.W., Sun, T.T., and Hayes, R.L.  $^{11}\text{C}$ -Labeled amino acids as agents for tumor and pancreas visualization. *J. Labelled Compounds and Radiopharmaceuticals* 13(2):203, 1977 (abstract).

Wieland, B.W., Washburn, L.C., Turtle, R.R., and Hayes, R.L. Development of cyclotron targetry and remote radiochemical techniques for the continuous large-scale production of  $^{11}\text{C}$ -labeled amino acids. *J. Labelled Compounds and Radiopharmaceuticals* 13(2):202, 1977 (abstract).

Washburn, L.C., Sun, T.T., Rafter, J.J., and Hayes, R.L. C-11-Labeled amino acids for pancreas visualization. *J. Nucl. Med.* 17:557-558, 1976.

Hayes, R.L., Washburn, L.C., Wieland, B.W., Sun, T.T., Turtle, R.R., and Butler, T.A. Carboxyl-labeled  $^{11}\text{C}$ -1-aminocyclopentanecarboxylic acid, a potential agent for cancer detection. *J. Nucl. Med.* 17:748-751, 1976.

Washburn, L.C., Coffey, J.L., Watson, E.E., Sun, T.T., and Hayes, R.L. Radiation dosimetry of some  $^{11}\text{C}$ -labeled amino acid pharmaceuticals. *In Radiopharmaceutical Dosimetry Symposium*, R.J. Cloutier, J.L. Coffey, W.S. Snyder, and E.E. Watson, eds., U. S. Dept. of Health, Education and Welfare, Washington, D.C., June 1976, pp. 441-451.

Hayes, R.L., Washburn, L.C., Sun, T.T., Rafter, J.J., and Byrd, B.L. Factors affecting the tissue distribution of  $^{11}\text{C}$ -ACPC, a new tumor-localizing agent. *In Proc. of 17th Annual Meeting, Southeastern Chapter, Society of Nuclear Medicine*, Louisville, Ky., 1976 (abstract).

Andrews, G.A., Hubner, K.F., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., and Butler, T.A. Clinical tumor scanning with  $^{11}\text{C}$ -carboxyl-labeled 1-aminocyclopentanecarboxylic acid ( $^{11}\text{C}$ -ACPC). *In Proc. of 17th Annual Meeting, Southeastern Chapter, Society of Nuclear Medicine*, Louisville, Ky., 1976 (abstract).

Hayes, R.L., Rafter, J.J., Washburn, L.C., and Byrd, B.L. Affinity of  $^{253}\text{einsteinium}$  for tumor tissue. *Nature New Biology* 246:23-25, 1973.

1079369

### 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 Raymond L. Hayes	TITLE Chief Scientist	BIRTHDATE (Mo., Day, Yr.) [REDACTED]	
PLACE OF BIRTH (City, State, Country) [REDACTED] Arizona USA	PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date) USA	SEX <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female	
EDUCATION (Begin with baccalaureate training and include postdoctoral)			
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HONORS [REDACTED]			
MAJOR RESEARCH INTEREST Radiopharmaceutical Development		ROLE IN PROPOSED PROJECT Consultant	
RESEARCH SUPPORT (See instructions)			

Total salary and research support through Department of Energy Contract Number DE-AC05-76OR00033.

**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.)

- 1950 - present Chief Scientist, Medical & Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, Tennessee.
- 1944 Senior Chemist, U. S. Rubber Co., Charlotte, North Carolina.

Publications:

- Hayes, R.L., Byrd, B.L., Rafter, J.J., and Carlton, J.E. The effect of scandium on the tissue distribution of Ga-67 in normal and tumor-bearing rodents. J. Nucl. Med. (in press).
- Hayes, R.L., Szymendera, J.J., and Byrd, B.L. Effect of food intake on the tissue distribution of gallium-67: Concise communication. J. Nucl. Med. 20:938-940, 1979.
- Digenis, G.A., Casey, D.L., Wesner, D.A., Washburn, L.C., and Hayes, R.L. Preparation of optically active C-11-amino acids. J. Nucl. Med. 20:662, 1979 (abstr.).
- Brown, D.H., Carlton, J.E., Rafter, J.J., and Hayes, R.L. A large scale extraction procedure for the purification of a Ga-67 binding glycoprotein. J. Nucl. Med. 20:682, 1979 (abstr.).
- Hayes, R.L., Rafter, J.J., and Byrd, B.L. Studies of the mechanism of gallium-67 uptake by tumor, abscess and normal tissues. J. Nucl. Med. 20:672-673, 1979 (abstr.).

1079370

NAME (last, first, middle initial)

Hubner, Karl F.

SOCIAL SECURITY NUMBER

Continuation page

Publications: R. L. Hayes (continued)

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. [Carboxyl-<sup>11</sup>C] 1-Aminocyclobutanecarboxylic acid, a potential tumor-seeking agent. J. Nucl. Med. 20:1055-1061, 1979.

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. DL-[Carboxyl-<sup>11</sup>C] tryptophan, a potential agent for pancreatic imaging: production and preclinical investigations. J. Nucl. Med. 20:857-864, 1979.

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., Butler, T.A., and Callahan, A.P. High-Level production of C-11-carboxyl-labeled amino acids. In Radiopharmaceuticals II, proceedings of 2nd International Symposium on Radiopharmaceuticals, Seattle, Wash., 1979, pp. 767-777.

Hubner, K.F., Andrews, G.A., Buonocore, E., Hayes, R.L., Washburn, L.C., Collmann, I.R., and Gibbs, W.D. Carbon-11-labeled amino acids for the rectilinear and positron tomographic imaging of the human pancreas. J. Nucl. Med. 20:507-513, 1979.

Brown, D.H., Carlton, J.E., Rafter, J.J., and Hayes, R.L. Further purification of a small <sup>67</sup>Ga-binding particle found in Morris 5123C hepatomas. Presented at the Sixth Annual Meeting of Southeastern Cancer Research Association, Kiawah Island, S. Carolina, November 15-17, 1978.

Hayes, R.L., Byrd, B.L., and Rafter, J.J. Studies of the mechanism of <sup>67</sup>Ga uptake by tumor and normal tissue. In Proc. of the 19th Annual Meeting, Southeastern Chapter, Society of Nuclear Medicine, held in Birmingham, Ala., November 1-4, 1978.

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. Further pre-clinical studies of C-11-DL-tryptophan, a potential pancreas-imaging agent. In Proc. of the 2nd International Congress of the World Federation of Nuclear Medicine and Biology, Washington, D.C., September 17-21, 1978, p. 41.

Kuniyasu, Y., Hayes, R.L., and Carlton, J.E. A Ga-68 albumin preparation for positron tomography of the liver. In Proc. of the 2nd International Congress of the World Federation of Nuclear Medicine and Biology, Washington, D.C., September 17-21, 1978, p. 90.

Hayes, R.L., Byrd, B.L., and Szymendera, J. Effect of food intake on the tissue distribution of gallium-67. In Proc. of the 2nd International Congress of the World Federation of Nuclear Medicine and Biology, Washington, D.C., September 17-21, 1978, p. 112.

Lawless, D., Brown, D.H., Hubner, K.F., Colyer, S.P., Carlton, J.E., and Hayes, R.L. Isolation and partial characterization of a <sup>67</sup>Ga-binding glycoprotein from a rat hepatoma. Cancer Res. 38:4440-4444, 1978.

Hayes, R.L. Chemistry and radiochemistry of metal-ion nuclides commonly employed in radiopharmaceuticals. In The Chemistry of Radiopharmaceuticals, N.D. Heindel, H.D. Burns, T. Honda, and L.W. Brady, eds. Masson Publishing, N.Y., 1978, pp.155-167.

Hayes, R.L. The medical use of gallium radionuclides: a brief history with some comments. Semin. Nucl. Med. 8:183-191, 1978.

DO NOT TYPE IN THIS SPACE-BINDING MARGIN

NAME (Last, first, middle, initial)

Hubner, Karl F.

SOCIAL SECURITY NUMBER

Continuation page

Publications: R. L. Hayes (continued)

Washburn, L.C., Sun, T.T., Anon, J.B., and Hayes, R.L. Effect of structure on tumor specificity of alicyclic  $\alpha$ -amino acids. *Cancer Res.* 38:2271-2273, 1978.

Hayes, R.L., Washburn, L.C., Wieland, B.W., Sun, T.T., Turtle, R.R., and Butler, T.A. Carboxyl-labeled  $^{11}\text{C}$ -l-aminocyclopentanecarboxylic acid, a potential agent for cancer detection. *Year Book of Cancer* 1978, pp. 236-237.

Hayes, R.L., Washburn, L.C., Wieland, B.W., Sun, T.T., Anon, J.B., Butler, T.A., and Callahan, A.P. Synthesis and purification of  $^{11}\text{C}$ -carboxyl-labeled amino acids. *Int. J. Appl. Radiat. Isotopes* 29:186-187, 1978.

Washburn, L.C., Wieland, B.W., Sun, T.T., Hayes, R.L., and Butler, T.A. [ $^{11}\text{C}$ ] DL-Valine, a potential pancreas-imaging agent. *J. Nucl. Med.* 19:77-83, 1978.

Washburn, L.C., Sun, T.T., Anon, J.B., and Hayes, R.L. Effect of structural modifications on the tumor specificity of alicyclic  $\alpha$ -amino acids. In Proc. of 18th Annual Meeting of Southeastern Chapter, Society of Nuclear Medicine, Part 2, Winston-Salem, N.C., October 12-15, 1977 (abstr.).

Hayes, R.L., Rafter, J.J., and Butler, T.A. Copper-64 as a possible positron tomographic agent for detection of cancer. In Proc. of 18th Annual Meeting of Southeastern Chapter, Society of Nuclear Medicine, Part 2, Winston-Salem, N.C., October 12-15, 1977 (abstr.).

Hayes, R.L., Carlton, J.E., and Kuniyasu, Y. A Ga-68 albumin preparation for positron tomography of the liver. In Proc. of 18th Annual Meeting of Southeastern Chapter, Society of Nuclear Medicine, Part 2, Winston-Salem, N.C., October 12-15, 1977 (abstr.).

Hayes, R.L. The tissue distribution of gallium radionuclides. *J. Nucl. Med.* 18:740-742, 1977.

Hubner, K.F., Andrews, G.A., Hayes, R.L., Poggenburg, J.K. Jr., and Solomon, A. The use of rare-earth radionuclides and other bone-seekers in the evaluation of bone lesions in patients with multiple myeloma or solitary plasmacytoma. *Radiology* 125(1):171-176, 1977.

Hubner, K.F., Andrews, G.A., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Winebrenner, J.D. Tumor location with l-aminocyclopentane [ $^{11}\text{C}$ ] carboxylic acid: preliminary clinical trials with single-photon detection. *J. Nucl. Med.* 18:1215-1221, 1977.

Andrews, G.A., Hubner, K.F., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Collmann, I.R. Clinical studies of C-11-labeled amino acids. *J. Nucl. Med.* 18:638, 1977 (abstr.).

Washburn, L.C., Wieland, B.W., Sun, T.T., and Hayes, R.L.  $^{11}\text{C}$ -Labeled amino acids as agents for tumor and pancreas visualization. *J. Labeled Compds. Radiopharmaceuticals* 13:203, 1977.

Wieland, B.W., Washburn, L.C., Turtle, R.R., Hayes, R.L., and Butler, T.A. Development of cyclotron targetry and remote radiochemical techniques for the continuous large-scale production of  $^{11}\text{C}$ -labeled amino acids. *J. Labeled Compds. Radiopharmaceuticals* 13(2):202, 1977.

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## 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 Paul Harvey King		TITLE Associate Professor		BIRTHDATE (Mo., Day, Yr.) [REDACTED]	
PLACE OF BIRTH (City, State, Country) [REDACTED] Indiana, USA		PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date) USA		SEX <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female	
EDUCATION (Begin with baccalaureate training and include postdoctoral)					
INSTITUTION AND LOCATION		DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD	
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]	
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]	
HONORS [REDACTED]					
MAJOR RESEARCH INTEREST Biomedical Engineering			ROLE IN PROPOSED PROJECT Consultant		
RESEARCH SUPPORT (See instructions)					

Total salary and research support through Vanderbilt University.

**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.)

July 1978 - July 1979 Sabbatical - Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN. (Presently a consultant).  
 1972 - present Associate Professor, Vanderbilt University, Nashville, TN.  
 Feb. 1971 - present Vanderbilt and Veterans Hospitals, Vectorcardiography research.  
 Aug. 1969 - present Vanderbilt and Veterans Hospital, Dynamics of bone healing, gait analysis.  
 Feb. 1966 - present Nuclear Medicine Dept., Vanderbilt Hospital, Nashville, TN.  
 Dec. 1966 - Sept. 1969 Kidney Dialysis Unit, Veteran's Hospital, Nashville, TN.  
 Sept. 1962 - Sept. 1965 Highland View Hospital (Metabolic Ward), Cleveland, Ohio.  
 June 1962 - Sept. 1962 Bell Aerosystems Co., (accelerometer research and design), Cleveland, Ohio.  
 June 1961 - June 1962 Case Institute of Technology (Asst. in Accelerometer Research), Cleveland, Ohio.

**Publications:**

Wieland, B.W., Highfill, R.R., and King, P.H. Proton accelerator targets for the production of  $^{11}\text{C}$ ,  $^{13}\text{N}$ ,  $^{15}\text{O}$ , and  $^{18}\text{F}$ . IEEE Transactions on Nuclear Sciences, Vol. NS-26(1):1713-1717, 1979.

Pickens, D.R., King, P.H., Patton, J.A., and Brill, A.B. The design, construction, and preliminary testing of a mutually orthogonal coincident focal point tomographic scanner, In Proc. of 13th Annual Meeting, Association for the Advancement of Medical

NAME (last, first, middle initial)

Hubner, Karl F.

SOCIAL SECURITY NUMBER

Continuation page

Publications: P. H. King (continued)

Instrumentation, Washington, D.C., March 29-April 1, 1978.

Smith, R.F., Stanton, K., Stoop, D., Brown, D., and King, P.H. Quantitative electrocardiography during extended spaceflight. Basic Environmental Problems of Man in Space, Ashton Grayziel, ed., Pergamon Press, 1976, pp. 89-102.

Smith, R.F., Stanton, K., Stoop, D., Janusz, W., and King, P.H. Quantitative electrocardiography during extended spaceflight: The second skylab mission. Aviation, Space and Environmental Medicine, April 1976, pp. 353-359.

Smith, R.F., King, P.H., Stanton, K., Stoop, D., and Brown, D. Quantitative electrocardiography during extended spaceflight. The first skylab mission. Astronautica Acta 2:89-102, 1975.

Patton, J.A., Brill, A.B., and King, P.H. A new mode of collection and display of three dimensional data for static and dynamic radiotracer studies. Proceedings of Symposium on Medical Radioisotope Scintigraphy 1972, Vol. 1, IAEA, Vienna, 1973, pp. 355-368.

Patton, J., Brill, A.B., and King, P.H. Transverse section brain scanning with multicrystal cylindrical imaging device. Conference on Radionuclide Tomography, Sept. 15, Tomographic Imaging in Nuclear Medicine. Society of Nuclear Medicine, New York, 1973, pp. 28-43.

King, P.H., Brill, A.B., Patton, J.A., Pickens, D.R., and Sweeney, J. Design of a new tomographic scanner. Conference on Computer Applications in Biomedical Instrumentation, June 6, 1972, at the University of Tennessee Space Institute, Tullahoma, Tennessee.

Patton, J.A., Brill, A.B., and King, P.H. A proposed method for quantitative blood flow transverse-section scanning. In Proceedings of Second Symposium on the Sharing of Computer Programs and Technology in Nuclear Medicine, Oak Ridge, Tennessee, USAEC CONF-720430, pp. 399-410.

King, P.H., Ginn, H.E., Baker, W.R., and Frost, A.B. Computer optimization of hemodialysis. In Conference on Computer Applications in Biomedical Instrumentation, June 5, 1972, at the University of Tennessee Space Institute, Tullahoma, Tennessee.

King, P.H., Patton, J., Pickens, D.R., Sweeney, J., and Brill, A.B. A multidetector orthogonally coincident focal point tomographic scanner. Sou. Med. J. 64(11):1422, 1971.

Brill, A.B., Johnston, R.E., Davies, H., King, P.H., Erickson, J., Williams, H., and Nash, R. Analysis of imaging techniques using digitally simulated scans. Sou. Med. J. 62, 1969.

Patton, J., Brill, A.B., Erickson, J., and King, P.H. Cylindrical array tomographic scanner with focusing collimators and its possible adaptation for fluorescence scanning of brain tumors. Sou. Med. J. 62:1434, 1969.

King, P.H., Ginn, H.E., Baker, W.R., Frost, A.B., and Matter, B.J. Computer optimization of urea dynamics during hemodialysis. Trans. Am. Soc. Artif. Int. Organs Vol. XIV, pp. 389-393, 1968.

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NAME (last, first, middle initial)

Hubner, Karl F.

SOCIAL SECURITY NUMBER

Continuation page

Publications: P. H. King (continued)

King, P.H., Baker, W., Day, R., Greenway, R., Lindan, O., and Reswick, J. Measurement of the random component ("noise") in the study of short term fluctuations in urine composition. In 19th Annual Conference on Engineering in Medicine and Biology, San Francisco, Calif., November 1966, Vol. 8, p. 203.

King, P.H., Brill, A.B., and King, R.J. Computer applications in nuclear medicine. J. Nucl. Med. 7:803, 1966.

King, R.J., Brill, A.B., King, P.H., and Kramer, C.E. A versatile isoresponse plotter with application in radiotherapy and nuclear medicine. Presented at 12th Annual Meeting American Nuc. Soc., Denver, Colorado, June, 1966.

King, P.H. Numerical Analysis and Data Processing in Metabolism Research. Master's Thesis, Case Institute of Technology, Cleveland, Ohio, 1965.

King, P.H. and Apple, H. Computer Oriented Study of Metabolism, Data Acquisition and Processing in Biology and Medicine, Paragamon Press, Vol. 4, 1964, pp. 23-36.

King, P.H., Apple, H., Baker, W., and Greenway, R. Metabolism data reduction in an on-line operation. In Proceedings of 17th Annual Conference on Engineering in Medicine and Biology, November, 1964, Cleveland, Ohio, p. 54.

Lindan, O., Baker, W., Greenway, R., King, P., and Reswick, J. Engineering approach in the design of experiments in human metabolism. In Proceedings of 17th Annual Conference on Engineering in Medicine and Biology, November, 1964, Cleveland, Ohio.

King, R.J., Brill, A.B., King, P.H., and Kramer, C.E. A digital data acquisition and analysis system for radionuclide scanning collimators. IBID, p. 803.

Paul H. King has 34 other publications, abstracts and presentations.

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1079375

**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.)

<b>NAME</b> I. Reid Collmann	<b>TITLE</b> Clinical Professor of Medicine	<b>BIRTHDATE (Mo., Day, Yr.)</b> [REDACTED]
<b>PLACE OF BIRTH (City, State, Country)</b> [REDACTED], Pennsylvania, U.S.A.	<b>PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)</b> U.S.A.	<b>SEX</b> <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female

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

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

**HONORS**  
[REDACTED]

<b>MAJOR RESEARCH INTEREST</b> Gastroenterology	<b>ROLE IN PROPOSED PROJECT</b> Consultant
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**RESEARCH SUPPORT (See instructions)**

None

Private practice - Gastroenterology.

**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.)**

- 1966 - present Clinical Professor of Medicine, University of Tennessee Memorial Research Center & Hospital, Knoxville, Tennessee.
- 1965 - present Chief, Department of Gastroenterology, University of Tennessee Memorial Research Center & Hospital, Knoxville, Tennessee.
- 1954 - 1965 Captain, MC, U. S. Army, 2nd General U. S. Army Hospital, Lanstuhl, W. Germany.

Publications:

Hubner, K.F., Andrews, G.A., Buonocore, E., Hayes, R.L., Washburn, L.C., Collmann, I.R., and Gibbs, W.D. Carbon-11-Labeled amino acids for the rectilinear and positron tomographic imaging of the human pancreas. J. Nucl. Med. 20:507-513, 1979.

Buonocore, E., Hubner, K.F., and Collmann, I.R. Differentiation of retroperitoneal tumor using positron emission computed tomography. J. Comput. Asst. Tomogr. 3(6): 825-828, 1979.

Andrews, G.A., Hubner, K.F., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Collmann, I.R. Clinical studies of C-11-labeled amino acids. J. Nucl. Med. 18:638, 1977 (abstr.).

1079376

NAME (Last, first, middle, initial)

Hubner, Karl F.

SOCIAL SECURITY NUMBER

Continuation page

Publications: I. Reid Collmann (continued)

Lange, R.D., Chernoff, A.I., Jordan, T.A., and Collmann, I.R. Experience with a hemagglutination-inhibition test for carcinoembryonic antigen: preliminary report. In Proceedings of the First Conference and Workshop on Embryonic and Fetal Antigens in Cancer, N.G. Anderson and J. H. Coggin, Jr., eds., 1971, pp. 379-386.

Peirce, E.C., II, Leshner, J.H., Law, W., and Collmann, I.R. Chronic occlusion of aortic arch branches. Dis. Chest 36:542-551, 1959.

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1079377

**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.)

<b>NAME</b> George A. Digenis	<b>TITLE</b> Prof. of Medicinal Chemistry Assoc. Prof. Nuclear Medicine	<b>BIRTHDATE (Mo., Day, Yr.)</b> [REDACTED]
<b>PLACE OF BIRTH (City, State, Country)</b> [REDACTED] Greece	<b>PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)</b> US. Citizen	<b>SEX</b> <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female

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

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

**HONORS**

[REDACTED]

<b>MAJOR RESEARCH INTEREST</b> Organic and Medicinal Chemistry, Biorganic Mechanisms and Radiopharmaceuticals	<b>ROLE IN PROPOSED PROJECT</b> Consultant
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**RESEARCH SUPPORT (See instructions)**

National Institutes of Health, "In Vivo Disposition of <sup>18</sup>F-haloperidol and <sup>82</sup>Br-bromperidol." \$38,477.  
 National Cancer Institute, "Physiologic Disposition of <sup>13</sup>N-Nitrosoureas and their Potential as Tumor Localizing Agents." No. P01-CA 17786, \$20,400.  
 University of Kentucky, Tobacco and Health Research Institute, "Disposition of <sup>13</sup>N-labeled Nitrosamines and Nitrosocarbamates." No. KTRB 011, \$41,772.

**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.)**

1974 - present Professor of Medicinal Chemistry and Associate Professor of Nuclear Medicine (1975-present) Colleges of Pharmacy and Medicine, University of Kentucky, Lexington, KY.  
 1976 - present Associate Scientist, Sloan Kettering Institute for Cancer Research, New York, N.Y.  
 Director of Radiopharmacy Program, College of Pharmacy, University of Kentucky, Lexington, KY.

Publications:

McQuinn, R.L., Feola, J., and Digenis, G.A. The effect of vitamin A on the uptake of a water soluble and lipid soluble nitrosourea by the EMT6 mouse mammary tumor. Int. J. Rad. Oncology, Biol. Physics 5:1577, 1979.

Digenis, G.A. and Issidorides, C.H. Some biochemical aspects of N-nitroso compounds. Bioorganic Chemistry 8:97-137, 1979.

McQuinn, R.L., Cherg, Y., and Digenis, G.A. Convenient preparations of several N-nitroso compounds. Synthetic Communications 9:25, 1979.

1079378

NAME (last, first, middle initial)

Hubner, Karl F.

SOCIAL SECURITY NUMBER

Continuation page

Publications - George A. Digenis (continued)

Papageorgious, V.P., Winkler, A., Sagredos, A.N., and Digenis, G.A. Studies on the relationship of structure to antimicrobial properties of naphthaquinones and other constituents of *alkanna tinctoria tausch*. *Planta Medica* 35:56, 1979.

Digenis, G.A., McQuinn, R.L., Freed, B., Tilbury, R.S., Reiman, R.E., and Cheng, Y.C. Preparation of  $^{13}\text{N}$ -labeled Streptozotocin and nitrosocarbaryl. *J. Labelled Compd. Radiopharmaceuticals* 16:95, 1979.

Triplett, J.W., Digenis, G.A., Layton, W.J., and Smith, S.L.  $^{13}\text{C}$ -NMR Studies of bisulfite-pyrimidine addition reactions: Stereoselective formation and reactions of the 5-halouridines. *J. Org. Chem.* 43:4411, 1979.

Martin, G.E., Shambhu, M.B., Shakhir, S.R., and Digenis, G.A. Polymer-bound carbonic-carboxylic anhydride functions. Preparation, site-site interactions and synthetic applications. *J. Org. Chem.* 43:4571, 1978.

Triplett, J.W., Chow, N.H., Smith, S.L., and Digenis, G.A. Determination of pK values for the bisulfite adducts of cytidine 5'-Monophosphate by carbon-13 nuclear magnetic resonance. *J. Org. Chem.* 43:3411, 1978.

Triplett, J.W., Chow, N.H., Smith, S.L., and Digenis, G.A. Carbon-13 NMR investigation of the bisulfite induced changes in yeast RNA. *Biochem. Biophys. Research Communications* 77(4):1170, 1977.

Triplett, J.W., Digenis, G.A., Layton, W.J., and Smith, S.L. Carbon-13 chemical shift assignments for the bisulfite adducts of uracil, 5-deuterouracil, 5-fluorouracil and 5-chlorouracil. *Spectroscopy Letters* 10:141, 1977.

Shambhu, M.B., Theodorakis, M.C., and Digenis, G.A. Polystyrene resins with immobilized polyamines: preparation, characterization, and ability to bind Cu (II) ions. *J. Poly. Sci. Chem.* 15:525, 1977.

Pettit, W.A., Tilbury, R.S., Digenis, G.A., and Mortara, R.H. A convenient synthesis of  $^{13}\text{N}$ -BCNU. *J. Labelled Compd. Radiopharmaceuticals* 13:119, 1977.

Triplett, J.W., Mack, S.W., Smith, S.L., and Digenis, G.A. Synthesis of carbon-13 labelled uracil, 6,7-dimethylumazine and lumichrome, via a common intermediate: cyanoacetylurea. *J. Labelled Compd. Radiopharmaceuticals* 14:35, 1978.

Digenis, G.A., Beihn, R.M., Theodorakis, M.C., and Shambhu, M.B. Use of  $^{99\text{m}}\text{Tc}$ -labeled triethylenetetramine-polystyrene resin for measuring the gastric emptying rate in humans. *J. Pharm. Sci.* 66:442, 1977.

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## SECTION II - PRIVILEGED COMMUNICATION

## BIOGRAPHICAL SKETCH

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

NAME Stephen Krauss	TITLE Director, Hematology-Oncology	BIRTHDATE (Mo., Day, Yr.) [REDACTED]	
PLACE OF BIRTH (City, State, Country) [REDACTED], Pennsylvania USA	PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date)	SEX <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female	
EDUCATION (Begin with baccalaureate training and include postdoctoral)			
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HONORS [REDACTED]			
MAJOR RESEARCH INTEREST Hematology-Oncology	ROLE IN PROPOSED PROJECT Consultant	Program in Dietetics	

## RESEARCH SUPPORT (See instructions)

Fifty percent research and other external support through NIH Grant Number CA 13237 - "Southeastern Cancer Study Group." Approved budget 08/01/79 - 07/31/80: \$124,373.

## 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.)

1970 - present University of Tennessee Memorial Research Center and Hospital, Knoxville, TN.; Assc. Prof. Research; Prof. of Medical Biology; Clinical Assoc. Prof. Medicine; Clinical Prof. Medicine.

1965 - 1970 Mt. Sinai School of Medicine, New York, N.Y.; Res. Assistant, Dept. of Hematology; Assoc. in Medicine; Asst. Prof. Medicine.

1964 - 1965 Research Instructor, State University of New York at Buffalo Medical School, Buffalo, New York.

1962 - 1965 US Public Health Service Senior Trainee (Hematology-Oncology), Roswell Park Memorial Institute, Buffalo, N.Y.

1959 - 1962 Residency (Hematology), Montefiore Hospital, New York.

1958 - 1959 Rotating Intern, Albert Einstein Medical Center, Philadelphia, PA.

## Publications:

Lowenbraun, S., Bartolucci, A., Smalley, R.V., Lynn, M., Krauss, S., Durant, J.R., and the Southeastern Cancer Study Group. The superiority of combination chemotherapy over single agent chemotherapy in small cell lung carcinoma. Cancer 44:406-413, 1979.

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RESEARCH PLAN

A. Specific Aims

Our overall objective is to evaluate the potential of using  $^{11}\text{C}$ -labeled natural and unnatural amino acids in conjunction with positron emission computerized tomography for the non-invasive differential diagnosis of pancreatic disease.

The use of radiopharmaceutical agents labeled with positron-emitting short-lived radionuclides makes possible external detection by coincidence counting techniques such as positron emission computerized tomography, which has the advantages of improved resolution and localization independent of depth. This approach offers a new non-invasive in vivo probe for quantitative and metabolic studies in man. It is particularly appealing because metabolic precursors and physiologically active compounds can be labeled with  $^{11}\text{C}$  ( $T_{1/2} = 20$  min) or  $^{13}\text{N}$  ( $T_{1/2} = 10$  min) without changing their biological properties; therefore, accurate external physiologic and metabolic observations that are otherwise only possible by autoradiography ( $^{14}\text{C}$ ,  $^3\text{H}$ ) or other invasive analyses of excised tissue can be made. Furthermore, the use of short-lived radionuclides permits sequential examinations over short time intervals without undue radiation exposure to the patient.

In selected patients with suspected cancer of the pancreas the uptake and distribution of  $^{11}\text{C}$ -labeled L-tryptophan or L-valine will be studied tomographically in order to determine whether in man the L-isomer localizes to a higher degree in normal pancreatic tissue than in neoplastic lesions of the pancreas, pancreatitis, pancreatic cysts, and benign tumors. (We have observed that DL-mixtures localize in both normal pancreas and in pancreatic carcinoma.) In order to use the L-form of  $^{11}\text{C}$ -labeled tryptophan or valine for clinical investigations, a method will have to be developed for resolving the DL-racemates of these  $^{11}\text{C}$ -labeled amino acids rapidly enough to be compatible with the short half-life of  $^{11}\text{C}$  (20.4 min). Both chromatographic and enzymatic procedures will be investigated.

Patients will also be examined with either  $^{11}\text{C}$ -1-aminocyclopentanecarboxylic acid ( $^{11}\text{C}$ -ACPC) or  $^{11}\text{C}$ -1-aminocyclobutanecarboxylic acid ( $^{11}\text{C}$ -ACBC), alicyclic unnatural amino acids that we have identified as tumor-localizing agents. The choice will be based on a determination of the agent having the higher uptake in pancreatic tumors relative to that in normal pancreas in man. Therefore, this research will test the potential of using  $^{11}\text{C}$ -labeled L-tryptophan or L-valine in conjunction with  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC for the differential diagnosis of pancreatic disease by positron tomography.

A further aim of this proposed work is to develop and test methods for the quantitative analysis of the in vivo distribution of  $^{11}\text{C}$ -labeled natural and unnatural amino acids in normal pancreas and specific sites of pancreatic disease. We propose to measure quantitatively amino acid extraction by pancreatic neoplasms before, during, and after chemotherapy and/or radiation therapy, i.e., to develop a model technique for objectively gauging response of pancreatic tumors to therapy based on metabolic parameters rather than on standard radiographic and subjective clinical evaluations. If applicable, this approach could avoid time-consuming chemotherapeutic protocol studies requiring large numbers of patients.

B. Significance

Carcinoma of the pancreas is now the fourth leading cause of death among cancer patients in the United States (1). It is usually diagnosed at an advanced stage. Although not yet proven, it is reasonable to assume that the prognosis for patients

Research Plan: Significance (continued)

with cancer of the pancreas could be improved through earlier diagnosis and treatment.

The development of computer-assisted tomography (CT) and ultrasound (US) have greatly improved the diagnostic assessment of pancreatic carcinoma, although the diagnostic accuracy is not better than 84% for CT or 80% for US, as was shown by Husband et al (2), and rarely are tumors measuring less than 2 cm in diameter detected by these methods. Other US studies by Feinberg et al (3) gave accurate diagnostic information in 93.8% of the cases. Haaga et al (4) diagnosed pancreatic neoplasms with CT correctly in 28 of 32 cases whereas US was incorrect in 3 of 7 patients. The accuracy of US in diagnosing pancreatic carcinoma varies considerably from laboratory to laboratory, but nevertheless US seems to be quite helpful as a screening method.

A nuclear medical technique employed with some success for diagnosis of pancreatic carcinoma involves imaging of the pancreas with a modified amino acid,  $^{75}\text{Se}$ -labeled L-selenomethionine. The pancreas is known to have a selective avidity for many amino acids (5). The use of a modified methionine is, however, not based on its avidity for pancreas so much as on the fact that methionine contains a sulfur atom which can be replaced by the gamma-emitting radionuclide  $^{75}\text{Se}$  without greatly altering the localization of the amino acid in the pancreas (6). With this technique cancers of the pancreas are seen as areas of decreased or absent uptake when the organ is visualized, usually by  $^{99\text{m}}\text{Tc}$ -colloid liver subtraction techniques (7). The procedure has been successful enough to become rather widely adopted, but it is far from ideal for several reasons: (1) the normal variability in the shape and position of the pancreas, (2) the presence of overlying organs anteriorly and posteriorly, (3) poorly explained variabilities in radiopharmaceutical concentration in the organ (in spite of various dietary regimens), and (4) high radiation dose to the patient due to the long physical half-life of  $^{75}\text{Se}$  (120 days) and the long biologic half-time of the agent (70 days). The general consensus appears to be that  $^{75}\text{Se}$ -L-selenomethionine scanning of the pancreas does not significantly contribute to the early diagnosis of cancer of the pancreas (8,9). Other extrastructurally labeled amino acids such as  $^{123}\text{I}$ -4-iodophenylalanine (10),  $^{123}\text{I}$ -5- and 6-iodotryptophan (10), and  $^{18}\text{F}$ -5- and 6-fluorotryptophan (11) have been synthesized but did not appear to be promising pancreas-scanning agents.

The work proposed in this application involves the use of  $^{11}\text{C}$ -labeled amino acids in the diagnosis of pancreatic diseases by positron emission computerized tomography. Although most naturally occurring amino acids show a significant affinity for the pancreas, two of them, tryptophan and valine, appear from animal studies to have the highest degree of pancreatic specificity (5, 12-14).

Washburn, Hayes, and co-workers of this laboratory have developed methods for synthesizing  $^{11}\text{C}$ -labeled amino acids (15,16), and our laboratory is at present the only one in the United States to have used these agents in positron tomographic clinical investigations. The production method, a rapid, high-temperature, high-pressure modification of the Bücherer-Strecker amino acid synthesis, gives racemic mixtures of  $^{11}\text{C}$ -labeled amino acids. (Reference 16, attached as Appendix A, gives details of the method.)

Up to this point our clinical experience with  $^{11}\text{C}$ -labeled tryptophan and valine has been restricted to the DL racemates (17,18) because resolution methods rapid enough to be compatible with the 20.4 min  $T_{1/2}$  of  $^{11}\text{C}$  have not been developed for these amino acids.

Research Plan: Significance (continued)

In order to accomplish the main task of this proposal, namely to develop a highly effective method for the differential diagnosis of pancreatic diseases, it is of utmost importance that we use the L-isomer of either  $^{11}\text{C}$ -labeled tryptophan or valine for positron tomography of the pancreas. The optical isomers of amino acids show distinctly different uptake behaviors in cancerous and normal pancreatic tissue. Tamemasa (19) has shown that the L-isomers have a high affinity for pancreas and other normal tissues, whereas the D-forms tend to localize preferentially in neoplastic lesions. Therefore, the DL-form would be expected to share the characteristics of both enantiomers and concentrate in normal pancreas and pancreatic tumors to an approximately equal degree. We have observed this type behavior with  $^{11}\text{C}$ -DL-tryptophan in our preliminary clinical studies. By using the L-optical form of tryptophan or valine, we feel we should be able to distinguish between functioning normal pancreas and any disease processes that are present. Malignant lesions could then be further differentiated from benign, cystic, and inflammatory processes by using either  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC, alicyclic unnatural amino acids that show preferential uptakes in tumor tissue but low affinities for inflammatory lesions (20). This non-invasive technique could thus provide for the differential diagnosis of pancreatic diseases, hopefully at an early stage.

Pancreas scanning with  $^{75}\text{Se}$ -L-selenomethionine and recent studies by Comar and co-workers (21) with  $^{11}\text{C}$ -L-methionine and positron tomography show that neoplastic lesions of the pancreas do appear as defects in the normal pancreatic image. (The production method for  $^{11}\text{C}$ -L-methionine, methylation of L-homocysteine with  $^{11}\text{CH}_3\text{I}$ , is not applicable to other  $^{11}\text{C}$ -labeled amino acids.) These findings, coupled with our own observations, have prompted our interest in using  $^{11}\text{C}$ -labeled L-tryptophan or L-valine as differential pancreas-scanning agents in conjunction with  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC.

In collaboration with Dr. G. Digenis of the University of Kentucky, we have successfully resolved  $^{11}\text{C}$ -DL-phenylalanine into its D- and L-isomers by oxidative deamination using immobilized L- and D-amino acid oxidase, respectively (22). The yields for  $^{11}\text{C}$ -D- and L-phenylalanine were 19 mCi and 27 mCi. Purification was accomplished by cation exchange chromatography, and the optical purity was established by optical rotatory dispersion. Resolution and purification required 35 minutes. This enzymatic method should be applicable to the resolution of other  $^{11}\text{C}$ -labeled amino acids, including  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine.

Several reports (23-25) have appeared recently concerning direct resolution of amino acid enantiomers by high pressure liquid chromatography (HPLC). Although resolution of  $^{11}\text{C}$ -labeled amino acids has not yet been reported, the technique seems ideal for this application. The most promising HPLC method involves use of a stationary phase made by coupling optically active proline to a suitable HPLC packing and then complexing with cupric ions. The potential advantages of the HPLC method are its speed of separation and the fewer manipulations that are required, relative to the enzymatic method. The technique does not appear to be general for all amino acids, but fortunately tryptophan and valine are among the amino acids most suited to the method (23).

Another method uses a classical HPLC packing and a chiral mobile phase. However, this method is difficult to use in a preparative way because of the problems encountered in separating the mixture obtained by solvent evaporation of the isolated fractions; therefore, according to Audebert (26), it is recommended only for analytical purposes.

Research Plan: Significance (continued)

Stewart and Doherty (27) have completely resolved DL-tryptophan by affinity chromatography on bovine-serum albumin-agarose columns. This resolution is based on a highly specific biological property, the antipodal specificity in the binding of tryptophan to bovine-serum albumin. This appears to be the method of choice for resolving  $^{11}\text{C}$ -DL-tryptophan. The disadvantage of this method is its lack of generality for other amino acids.

The development of a method for rapidly resolving the L-form of amino acids from their DL-racemates as proposed in this project would be a significant contribution to basic research into the function of the human pancreas and to research in amino acid metabolism in general. It would open the door to in vivo assessment of uptake, kinetics and metabolism of natural, metabolizable amino acids in organs such as brain, heart, and liver, as well as the pancreas.

The success of the project depends on progress in the resolution of  $^{11}\text{C}$ -amino acid racemates but equally important is the development of computer capability and the acquisition of an updated ECAT scanner (equivalent to ECAT II). Correct staging of malignant tumors and objective evaluation and measurement of the response of tumors to therapy is not always possible. It is especially difficult to measure regression of tumors early after initiation of therapy, and a method that allows objective external measurement of biological/metabolic changes induced by treatment would be highly desirable. In this proposed research we will attempt to develop a biologic "caliper" to measure pancreatic tumor response to therapy by using quantitative positron emission computerized tomography to measure the fraction of  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC extracted by a tumor. This kind of tomographic test would be an extremely useful research tool for monitoring therapy, and it could be the basis for a later development of a simple test using conventional external counting methods.

C. Preliminary Studies

On the basis of the partial success of diagnostic procedures with radiopharmaceuticals such as  $^{75}\text{Se}$ -L-selenomethionine, we have undertaken to try a series of related diagnostic methods that take advantage of several potential improvements:

(a) As stated above, certain amino acids show a greater tendency to concentrate in the pancreas than does  $^{75}\text{Se}$ -L-selenomethionine. In animal work carried out by ourselves (13,14) and others (5,12), both DL-tryptophan and DL-valine have been shown to have a high affinity for the pancreas. We have shown that these  $^{11}\text{C}$ -labeled amino acids can be rapidly synthesized and purified in quantities adequate for pancreas visualization in animals and man (15,16). Table 1 shows our production experience for the four  $^{11}\text{C}$ -labeled amino acids discussed in this proposal. (The method is quite general and is useful for production of many other  $^{11}\text{C}$ -labeled amino acids.) We are able to produce multiple batches of  $^{11}\text{C}$ -labeled amino acids at intervals of 1 hr or less by overlapping the various steps, i.e., generation of  $^{11}\text{C}$  activity, amino acid synthesis, amino acid purification, and column regeneration. In a typical all-day run, we routinely produce four or more batches of various  $^{11}\text{C}$ -labeled amino acids for clinical or preclinical investigation.

(b) We can take advantage of the special radiation characteristics of  $^{11}\text{C}$ . Decay by positron emission is accompanied by the production of two annihilation photons emitted at an angle of  $180^\circ$  to each other. Using recently developed instrumentation that utilizes these coincident annihilation photons and the techniques associated with transmission computerized tomography, it is possible to reconstruct cross-sectional images that show three-dimensionally the source of positron-emitting activity in the body (28,29). The distinct advantage of this type of imaging is that

Research Plan: Preliminary Studies (continued)

Table 1  
 $^{11}\text{C}$ -Labeled Amino Acid Production at M&HSD/ORAU  
 (Through March 4, 1980)

Amino Acid	Total Number Batches	Number Patients Studied	Average Activity (mCi/batch)	Highest Yield (mCi)
$^{11}\text{C}$ -DL-Valine	38	18	160	360
$^{11}\text{C}$ -DL-Tryptophan	57	51	118*	330
$^{11}\text{C}$ -ACPC	76	59	96*	300
$^{11}\text{C}$ -ACBC	43	36	135	420

\* In early development of these compounds the yields were low.

it provides high resolution and avoids image distortion due to surrounding radioactivity. Furthermore, the image obtained is subject to quantitative analysis (30). The Medical and Health Sciences Division of Oak Ridge Associated Universities has had a commercially available positron emission computerized tomographic scanner (ECAT I) available for clinical investigations since May 1977. By combining the advantages of  $^{11}\text{C}$ -labeled DL-tryptophan or DL-valine with this optimal-type imaging, it was anticipated that greatly improved pancreatic diagnostic results could be obtained. Carcinomas were expected to be seen as areas of decreased or absent concentration as is the case with  $^{75}\text{Se}$ -L-selenomethionine.

(c) Based on this concept, we also developed a method for labeling the unnatural alicyclic amino acids l-aminocyclopentanecarboxylic acid (ACPC) and l-aminocyclobutanecarboxylic acid (ACBC) with  $^{11}\text{C}$  because of their potential as tumor-localizing agents, particularly when used in conjunction with positron tomography (31,32). Thus  $^{11}\text{C}$ -ACPC and  $^{11}\text{C}$ -ACBC were developed for confirmation of suspected malignancies seen on  $^{11}\text{C}$ -DL-tryptophan or  $^{11}\text{C}$ -DL-valine scans of the pancreas.

Our results have shown that positron emission computerized tomographic (ECT) imaging of the pancreas with  $^{11}\text{C}$ -carboxyl-labeled DL-tryptophan and DL-valine allows physiologic studies by imaging and has the potential to measure in vivo the utilization of metabolic substrates or analogs. Positron tomographic studies (examples are shown in Appendix B) supplement the morphologic information obtained by ultrasound (US) and transmission computerized tomography (CT). A group of 29 patients with proven or suspected pancreatic disease were examined with positron ECT; 18 of these subjects were also studied with US and transmission CT. In 26 patients with known clinical outcomes, positron ECT gave one false positive and three false negative results (17). Ultrasound and/or transmission CT failed to show three proven lesions. Uptake of  $^{11}\text{C}$ -DL-tryptophan clearly delineated three pancreatic carcinomas and one lymphoma. In normal subjects positron tomography with these agents invariably showed the pancreas with striking clarity. These observations indicate that positron tomography provides a unique method for visualizing biologic activity and that quantitative analysis of amino acid utilization should be possible with this non-invasive technique. The fact that selective pancreatic localization of these agents occurs almost immediately after intravenous injection means that the short half-life of  $^{11}\text{C}$  rather than being a disadvantage is on the contrary actually an asset in terms of lowered radiation dose and the possibility of frequent repetition of scans.

Our finding that the racemic forms of  $^{11}\text{C}$ -valine and  $^{11}\text{C}$ -tryptophan localized to a significant degree in pancreatic neoplasms was unexpected. We had expected to see

Research Plan: Preliminary Studies (continued)

carcinomas as zones of decreased or absent concentration as is the case with  $^{75}\text{Se}$ -L-selenomethionine. Especially in view of findings published by Tamemasa et al (19), it is likely that the presence of the D isomer is responsible for the tumor affinity observed with the amino acid racemates we used in our studies.

We have shown the general usefulness of the unnatural amino acid  $^{11}\text{C}$ -ACBC as a tumor-localizing agent in conjunction with positron tomography. Our present experience with  $^{11}\text{C}$ -ACBC is limited to 36 patients. The variety of neoplasms that concentrate  $^{11}\text{C}$ -ACBC very rapidly after intravenous injections includes bronchogenic carcinoma, metastatic mammary Ca, Ca of the stomach, lymphomas (33), and poorly differentiated carcinomas, as well as cancer of the pancreas.  $^{11}\text{C}$ -ACBC cannot be metabolized and shows promise as a useful tool for measuring the metabolic activity and/or the proliferative stage of tumors.

An important factor in the total success of our proposed project involves quantitation using an ECAT positron emission computerized tomograph. In the course of over two years experience in patient studies and as a result of intentional computer program challenges in phantom studies, we have observed some serious deficiencies in the performance of our ECAT; i.e., phantom studies indicate that reconstructed data, in terms of calculated image "quantity" versus "dose", is not a linear function. The amount of isotope measured in a particular region of a reconstructed image is both a function of the image size (34) and the amount of positron emitter present (a non-linear function, due to randoms)! The "measured" amount of activity in an area as a function of time, if the effect of count rate were to be ignored, is of little significance in the pancreas, as the size of that organ does not change significantly. However, the ability of the pancreas to extract the various labeled agents which we propose to use, and therefore the relative amount of Compton and random scatter contributing to a calculation of relative isotope uptake, will influence our measurement of the rate of suppression (or lack thereof) of the cancerous tissues' growth. Our experience with calculations on phantoms has dramatically shown the effect of both image size (equivalent in part to tumor size) and count rate (equivalent to tumor uptake) on quantification of our results. A 30% or greater variation in count rate per  $\text{cm}^2$  has not been uncommon in our data, despite efforts to correct the data for known non-linearities.

We have improved on the basic software provided with the original ECAT I system, initiating procedures involving multi-level transmission image data correction, Compton scatter correction, outlier data squelching, background subtraction routines, etc., but we are still in need of better data, as collected, to quantify and confidently analyze our results in a quantitative manner.

A new version of the ECAT, ECAT II, overcomes to a great extent the problems we have encountered with our ECAT I (35). We, therefore, propose to update our ECAT I electronically to an ECAT II and have accordingly included funds in our proposal to accomplish this during the first year of the project. Preliminary evidence of attempts to improve the quantitative capabilities as outlined under Methods: "Improvement of Quantitative Imaging" suggests that not all the problems will be completely corrected. But any corrections devised for ECAT I will also be applicable to ECAT II.

Research Plan:

D. Methods

Resolution of  $^{11}\text{C}$ -labeled amino acids

An essential part of this proposal is the development of analytical techniques for rapidly resolving the racemic mixtures of  $^{11}\text{C}$ -labeled amino acids which result from the modified Bücherer-Strecker synthesis. Our production method (16) has produced (Table 1) up to 330 mCi of  $^{11}\text{C}$ -DL-tryptophan and 360 mCi of  $^{11}\text{C}$ -DL-valine in a total synthesis and purification time of 40-45 min, one-half of which is devoted to synthesis and the other half to chromatographic purification. (See Appendix A for details.) Because of our high production capability, we should, therefore, be able to separate the L-isomers from these racemates and still have more than an adequate amount of  $^{11}\text{C}$ -labeled L-tryptophan or L-valine for clinical studies ( $\sim 10$ -15 mCi will be required).

We propose to combine resolution and purification through use of recently developed chromatographic or enzymatic techniques. This should result in an overall synthesis, resolution, and purification time which is compatible with the 20.4 min half-life of  $^{11}\text{C}$ . This production time could, in fact, be no longer than the 40-45 min currently required for  $^{11}\text{C}$ -labeled racemic amino acids.

Based on our initial clinical studies of  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine (see Preliminary Studies) and animal studies by both our group (13,14) and others (5,12), tryptophan appears to be considerably more specific for the pancreas than valine. Proposed studies during the first year of support will further compare the two agents (see following section on proposed clinical investigations). If  $^{11}\text{C}$ -DL-tryptophan is indeed shown to be superior, our resolution efforts will be concentrated on this agent. Resolution of  $^{11}\text{C}$ -DL-valine will be attempted only if attempts to resolve  $^{11}\text{C}$ -DL-tryptophan are unsuccessful.

The method of choice for resolution of  $^{11}\text{C}$ -DL-tryptophan appears to be affinity chromatography on bovine-serum albumin-agarose columns as reported by Stewart and Doherty (27). The stationary phase is prepared by linking defatted bovine-serum albumin to cyanogen bromide-activated Sepharose 4B by an ethylenediamine-succinic acid leash. The method is highly specific for resolving DL-tryptophan, utilizing the differential binding constants of bovine-serum albumin for the optical antipodes of this amino acid. The column is equilibrated with pH 9.2 0.1 M borate buffer, the racemic tryptophan mixture is loaded, and D-tryptophan is eluted with the same 0.1 M borate buffer. L-Tryptophan is then eluted with 0.1 M acetic acid. Excellent resolution was obtained with 500 nmol of DL-tryptophan on a 0.9 x 25-cm column with a flow rate of 30 ml/hr. For resolution of  $^{11}\text{C}$ -DL-tryptophan at the reaction scale now used (0.1 mmole), a larger column will be required, probably on the order of 2.5 x 25 cm. Column flow rates will be increased by using 7-9 psi of positive air pressure, as we currently do for our other column separations (16). It should be possible to use the bovine-serum albumin-agarose affinity column as a preliminary purification step (in place of the Porapak Q column which we now use), followed by cation-exchange chromatography for final purification and concentration of the  $^{11}\text{C}$ -L-tryptophan solution.

A product called CH-Sepharose 4B is available from Pharmacia Fine Chemicals which has free carboxyl groups at the end of 6-carbon spacer arms. Ligands containing primary amino groups can easily be coupled by the carbodiimide procedure. The concentration of spacer arms is 10-14  $\mu\text{moles}$  per ml of swollen gel. Use of this

Research Plan: Methods (continued)

commercial product may be preferable to the procedure of Stewart and Doherty because the concentration of spacer arms and thus the concentration of coupled protein can be made uniform from batch to batch. The size of the spacer arms is similar in the two products and thus similar resolution results should be obtained.

If the resolution of  $^{11}\text{C}$ -DL-tryptophan described above should unexpectedly fail, high pressure liquid chromatographic (HPLC) methods will be employed for resolution of this amino acid or  $^{11}\text{C}$ -DL-valine. Many reports have appeared in the literature in recent years concerning the use of chiral stationary phases for the direct resolution of racemates by ligand-exchange chromatography (23-25). For resolution of amino acid racemates, an optically active amino acid, usually L-proline, is coupled to a stationary phase suitable for HPLC and the resulting resin is complexed with metal ions, normally cupric ions. The modified stationary phase is then packed into an HPLC column by conventional techniques. The mobile phase is typically water or an aqueous buffer system. With L-proline, the D-amino acid is usually eluted first, but it should be possible to reverse this order and thus save time by using D-proline instead of L-proline in the preparation of the stationary phase. The work to date with these methods has been limited to analytical applications; however, by using larger, semi-preparative HPLC columns, it should be possible to resolve  $^{11}\text{C}$ -labeled amino acid racemates at the 0.1 mmole reaction scale which we generally use. The HPLC method may be used by itself or it may be necessary to use the method for resolution and preliminary purification, followed by final purification and concentration using cation-exchange chromatography, as discussed above for affinity chromatography.

We have communicated (Appendix C) with Drs. B. Lefebvre and R. Audebert of Laboratoire de Physico-Chimie Macromoléculaire, l'Université Pierre et Marie Curie, Paris, France, about the availability of a chiral hydrophilic gel which they used with great success in the resolution of several racemic amino acid mixtures (24). These researchers kindly replied (Appendix D) that the hydrophilic packing is to be manufactured by an industrial firm in the near future and promised to send us a sample when it becomes available.

Should the chromatographic methods described above not be successful for resolving  $^{11}\text{C}$ -DL-tryptophan or  $^{11}\text{C}$ -DL-valine, we will use the enzymatic method developed by Dr. G. Digenis of the University of Kentucky School of Pharmacy in collaboration with our research group (22). Dr. Digenis has agreed to act as a consultant to this project at no charge (see Biographical Sketch). The method has to date been used only for resolution of  $^{11}\text{C}$ -DL-phenylalanine but should be quite easily adaptable to other  $^{11}\text{C}$ -labeled amino acid racemates, including  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine. The procedure involves oxidative deamination using the appropriate immobilized amino acid oxidase (AAO); i.e., if the L-enantiomer is desired, as in the proposed clinical studies, the immobilized D-AAO would be used to cause selective degradation of the unwanted D-enantiomer. For the  $^{11}\text{C}$ -DL-phenylalanine resolution studies, L-AAO was immobilized on diazotized arylamine glass beads and D-AAO was bound to cyanogen bromide - activated Sepharose 4B. Immobilized L-AAO and D-AAO were incubated at 37° with buffered  $^{11}\text{C}$ -DL-phenylalanine solutions at pH's of 6.8 and 9.0, respectively. The optically active amino acid in each case was separated from phenylpyruvic acid (the product of oxidative deamination) by cation-exchange chromatography. In the  $^{11}\text{C}$ -DL-phenylalanine studies, the resolution and purification were done on a previously purified racemic amino acid solution. Therefore, 35 min was required in addition to the 40-45 min needed for production of the purified  $^{11}\text{C}$ -amino acid racemate, for a total of 75-80 min. We will evaluate the feasibility of eliminating the preliminary separation steps and using the crude

Research Plan: Methods (continued)

reaction mixture directly for enzymatic resolution. This would result in a saving of ~ 20 minutes, giving a net production time of 55-60 min, which is compatible with the short half-life of  $^{11}\text{C}$ .

The proposed schedule for resolution of  $^{11}\text{C}$ -labeled amino acids is as follows: (1) During the first year the various resolution methods will be evaluated largely using unlabeled compounds. A limited number of developmental cyclotron runs would also be required during the latter part of the first grant year. (2) In the second year of grant support, technique development will be completed, requiring an increased number of developmental cyclotron runs. Tissue distribution studies using the  $^{11}\text{C}$ -labeled resolved amino acid to be studied clinically will be performed in two animal species in support of an Investigational New Drug (IND) application to be filed with the U.S. Food and Drug Administration; the agent will then be made available for clinical use during the latter part of the second grant year. (3) During the third grant year the  $^{11}\text{C}$ -labeled resolved amino acid will be made available for continued clinical trials.

Clinical Investigation

Clinical investigations using  $^{11}\text{C}$ -labeled amino acids in conjunction with positron emission computerized tomography will be divided into three phases over the 3-year study period.

During the first year emphasis will be placed on comparison of  $^{11}\text{C}$ -ACPC and  $^{11}\text{C}$ -ACBC and of  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine with regard to differential uptake in pancreas versus tumor in patients with strongly suspected pancreatic carcinoma. By the end of the first year the updated ECAT scanner (ECAT II) will be available for clinical use and our studies will be expanded beyond imaging into quantitative measurements of amino acid concentrations in pancreatic tumors before, during, and after treatment (see Quantitative Imaging). Late in the second year the  $^{11}\text{C}$ -labeled L-form of tryptophan or valine is expected to be available for clinical use. These clinical studies will then be completed in the third year.

Clinical investigations in the first year will first focus on comparing  $^{11}\text{C}$ -ACPC and  $^{11}\text{C}$ -ACBC using positron tomography in patients with suspected pancreatic carcinoma to determine whether  $^{11}\text{C}$ -ACPC might have an advantage over  $^{11}\text{C}$ -ACBC in the diagnosis of pancreatic tumors. Our previous experience with  $^{11}\text{C}$ -ACPC and rectilinear scanning (20) has shown that little  $^{11}\text{C}$ -ACPC is taken up by the human pancreas, but high concentrations of this unnatural amino acid have been observed in pancreatic tumors. On the other hand  $^{11}\text{C}$ -ACBC seems to concentrate almost as well in normal pancreas as in tumors of the pancreas.  $^{11}\text{C}$ -DL-Tryptophan and  $^{11}\text{C}$ -DL-valine will be similarly compared to further investigate the apparently greater pancreatic specificity of  $^{11}\text{C}$ -DL-tryptophan found in preliminary studies.

In a separate study, we are planning to investigate the efficacy of  $^{11}\text{C}$ -labeled amino acids in conjunction with positron tomography for assessing the response of pancreatic carcinoma to therapy. This group of patients will be examined before, during and after therapy with  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC and  $^{11}\text{C}$ -DL-tryptophan or  $^{11}\text{C}$ -DL-valine (depending on the results of the initial comparison of the two pairs of amino acids). Quantitation of amino acid distribution in the pancreas or tumors will be accomplished by placing a reference source containing a known fraction of the dose in the field of view during the patient scans. The reference source will be contained in a disposable 60 cc syringe having a diameter of 2.8 cm. The radioactive solution in the syringe will extend across the entire plane of the field of view of the

Research Plan: Methods (continued)

detector system (3.7 cm). Patient scans will be done with 9 mm spacing between planes. When a region of the pancreas or a tumor is demonstrated in three consecutive planes, the center plane will be used for quantitative analysis. Counts in a region of interest will be compared to the counts in the reference source to quantitate activity. Results will be expressed in  $\mu\text{Ci}/\text{cm}^3$ . The protocol for the first year is outlined in the following table (Table 2):

Table 2  
Clinical Investigations During First Year

<u>No. Patients</u>	<u>Patient Selection Criteria</u>	<u>Scanning Agent</u>
10	Strongly suspected pancreatic Ca (pain, weight loss, anorexia and possibly jaundice)	$^{11}\text{C}$ -ACPC and $^{11}\text{C}$ -ACBC on same day before surgery or biopsy
5	As above	$^{11}\text{C}$ -DL-tryptophan and $^{11}\text{C}$ -DL-valine on same day before surgery or biopsy
5	Patients receiving chemotherapy and/or radiation therapy for pancreatic Ca*	$^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) and $^{11}\text{C}$ -DL-tryptophan (or $^{11}\text{C}$ -DL-valine) on same day x 3

\* Positron tomography scans with the two preferred scanning agents will be done before, during and after a course of therapy.

Table 3 lists the clinical information needed for the patients selected for the studies outlined in Table 2.

Table 3  
Clinical Information Required

<u>General</u>	<u>Laboratory Tests</u>	<u>Radiographic Studies (not mandatory)</u>	<u>Experimental Studies</u>	<u>Acceptable Confirmatory Examinations</u>
History and Treatment	Serum amylase Urine amylase CEA Lipase	GI series Barium enema Gallbladder	Transmission CT Ultrasound ECAT positron tomography Endoscopy	ERCP with cytology Directed biopsy Surgery Subcutaneous cholangiogram Arteriogram

The endpoints of the first year's studies will be the following:

1. Decision on the superiority of  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACEC for selectively imaging pancreatic cancer with positron tomography.
2. Decision on the superiority of  $^{11}\text{C}$ -DL-tryptophan or  $^{11}\text{C}$ -DL-valine for imaging normal pancreatic tissue with positron tomography.
3. Complete scan data collection on five patients receiving treatment for pancreas carcinoma for quantitative analysis during second year of funding period with ECAT II capability.
4. Confirm diagnosis.
5. Determination of morbidity and risk factors.

During the second year we anticipate that we will have available a quantitative ECAT II system for in vivo metabolic studies in patients with pancreatic cancer and chronic relapsing pancreatitis. Use of the updated ECAT system (ECAT II) should not

Continuation page

Research Plan: Methods (continued)

only yield data amenable to quantification, but should also give us the advantage of simultaneous image reconstruction cojoint with image acquisition; this will allow for immediate rescanning, thus providing efficiency in instrument use. In the second year we will expand the series of quantitative in vivo studies by 10 patients in the pancreas cancer therapy group and also study 10 patients with chronic pancreatitis during different phases of their disease. Each patient will be examined three times during the course of the disease as outlined in Table 4.

In addition, we project that  $^{11}\text{C}$ -L-tryptophan (or  $^{11}\text{C}$ -L-valine) will become available for clinical use during the latter part of the second grant year. Therefore, five patients with suspected pancreatic carcinoma will be studied using  $^{11}\text{C}$ -L-tryptophan (or  $^{11}\text{C}$ -L-valine) in conjunction with  $^{11}\text{C}$ -ACPC (or  $^{11}\text{C}$ -ACBC) in a preliminary test of this regimen for differential diagnosis of pancreatic carcinoma.

Table 4  
Clinical Investigations During Second Year

<u>No. Patients</u>	<u>Patient Selection Criteria</u>	<u>Scanning Agents</u>
10	Patients receiving chemotherapy and/or radiation therapy for pancreatic Ca*	$^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) and $^{11}\text{C}$ -DL-tryptophan (or $^{11}\text{C}$ -DL-valine) x 3
10	Patients with chronic pancreatitis*	$^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) and $^{11}\text{C}$ -DL-tryptophan (or $^{11}\text{C}$ -DL-valine) x 3
5	Patients with suspected pancreatic Ca	$^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) and $^{11}\text{C}$ -L-tryptophan (or $^{11}\text{C}$ -L-valine)

\* Positron tomography scans will be done with the two preferred scanning agents at several stages of the disease.

The clinical information needed is the same as that indicated in Table 3. Endpoints of the studies projected for the second year are to:

1. Determine the effect of successful treatment and tumor progression on the uptake of  $^{11}\text{C}$ -ACPC (or  $^{11}\text{C}$ -ACBC) and  $^{11}\text{C}$ -DL-tryptophan (or  $^{11}\text{C}$ -DL-valine) in patients undergoing therapy for pancreatic carcinoma.
2. Determine the effect of the phase of pancreatitis on the uptake of the same agents.
3. Determine whether ECAT II techniques can be applied to quantitate accurately amino acid extraction/utilization by tumors of the pancreas.
4. Determine whether the prognostic information obtained with this approach corresponds with the clinical response to therapy.

During the third year clinical studies with  $^{11}\text{C}$ -L-tryptophan (or  $^{11}\text{C}$ -L-valine) in conjunction with  $^{11}\text{C}$ -ACPC (or  $^{11}\text{C}$ -ACBC) to determine the potential of this method for the non-invasive, accurate diagnosis of pancreatic carcinoma will be completed. In addition the quantitative studies in patients undergoing treatment for pancreatic carcinoma will continue through the third year. The outline for the clinical studies during the third year is given in Table 5.

Continuation page

Research Plan: Methods (continued)

Table 5  
Clinical Investigations During Third Year

<u>No. Patients</u>	<u>Patient Selection Criteria</u>	<u>Scanning Agents</u>
10	Suspected pancreatic carcinoma	$^{11}\text{C}$ -L-tryptophan (or $^{11}\text{C}$ -L-valine) and $^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC)
15	Patients with proven pancreatic carcinoma undergoing chemotherapy*	$^{11}\text{C}$ -L-tryptophan (or $^{11}\text{C}$ -L-valine) and $^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) x 3

\* Patients in this group will be scanned one time each before, during and after the first course of cyclic chemotherapy.

Endpoints of clinical investigations in the third year will be to:

1. Verify in humans the potential utility of positron tomography using a combination of a natural  $^{11}\text{C}$ -labeled L-amino acid to visualize the normal pancreas and an unnatural  $^{11}\text{C}$ -labeled amino acid for the differential diagnosis of pancreatic disease.
2. To provide evidence that in vivo measurements of amino acid extraction/ utilization by pancreatic cancer could be applied to accurately gauge the response of such cancers to therapy.
3. To collect information for a comparative cost analysis between conventional staging and gauging procedures used in developmental chemotherapy protocols and the in vivo measurements of the proliferative activity of pancreatic cancers as planned for this proposal.

#### Improvement of Quantitative Imaging

It is well recognized that unwanted scattered radiation events occur as a function of scattering medium and count rate. True coincidence counting and the development of high quality images and accurate quantitation is the goal of positron tomography systems with their associated computational programs.

In our present system (ECAT I), singles, accidental coincidences, and scattered coincidence events tend to mask the true coincidence data. Extraneous events, accepted as true events, have accounted for up to 60% of the data collected in scans of phantoms using this system.

In several of our phantom studies we have made attempts to linearize the response of our system to known concentration levels in the field of view. Computation techniques used have included background subtraction of data from the collected images and the development of software to estimate body densities and produce a refined body attenuation estimate for use in back projection algorithms.

Consistently, we have found that whatever technique we use, our correction scheme must take into account the total count rate of the system. For example with a low count rate phantom we found it best to back project using an 8% background subtract figure, but the same phantom required almost a 16% correction when the phantom count rate was four times as high.

1079395

Research Plan: Methods (continued)

The addition of a delayed coincidence gate and other associated hardware and software improvements available in the ECAT II system would allow us to estimate the amount of "random" coincidences occurring in the image as it is collected and permit real time or later "randoms" correction. While this technique will not remove all unwanted events, it will tend to linearize the system with respect to its present intensity versus count rate nonlinearities.

We shall specifically therefore continue software development which will yield improved images, by acquiring experience with both patient and phantom studies, and applying and upgrading our analysis schemes. Our present schemes, as mentioned, include operations such as background subtract, outlier squelching, normalization, transmission data file manipulation, etc. It is anticipated that some combination of these methods, including perhaps an as yet untried Compton scattering correction routine, will yield a computational protocol which will be invariant from phantom to phantom, count rate independent, and linear.

Listed below are some of the computation techniques we will study:

1. Emission Data Corrections:
  - a. Background subtraction techniques
    - (1) Constant value
    - (2) Percentage of maximum
    - (3) Ramp(s) calculated from data files to edge of body
    - (4) Combinations of 1,2,3
    - (5) Nonlinear amount based upon square of count rate
  - b. Blanking outside body outline
2. Transmission Data Corrections
  - a. Single level transmission data estimation
  - b. Multilevel body outline estimation
  - c. Data bounding, smoothing
3. Transmission-corrected Emission Data
  - a. Data bounding (outlier squelching)
  - b. Data projection normalization
  - c. Randoms subtraction (linear and nonlinear)

Our approach to quantification will include detailed studies on the effects of scattered radiation on the quality of our collected data. For example, a typical human torso, if modeled as an ellipse, might be 15 cm along the short axis and 30 cm along the long axis. A point source, located at the origin of this ellipse, would not be equally sensed in all projections, due to varying thicknesses of material between the source and sensor. In fact, using an attenuation coefficient of  $0.1 \text{ cm}^{-1}$ , only 7.4 to 22.5% of the radiation would be sensed in any given projection, compared to the non-attenuated case.

Continuation page

Research Plan: Methods (continued)

At 511 keV, for water, only 35% of incident gamma rays are absorbed in Compton scattering, the remainder are primarily forward scattered albeit at a degraded energy level. It is apparent from our phantom studies that some of this forward scattered radiation must be being detected, as calculations on both emission and transmission data show increases in count rate levels over that predicted by theory for phantoms with attenuation. This data has been confirmed both by comparing sensed radiation levels for various phantoms involving several levels of activity, and by comparing transmission data through known thicknesses of water with that of air. Further, from observation of all phantom and patient data, we note that radiation is sensed in all areas of the initial data files where there is only air present.

Preliminary data has indicated to us that the Compton scattering phenomena, at least as measured in air outside our phantoms, might be mathematically modeled as arising from a convolution of an exponential function with an apparent true distribution. The rate of fall of the exponential function seems somehow to be related to the attenuation properties of the phantom. An explanation for this behavior will be one of our goals.

E. Facilities Available1. Laboratory space

Our equipped radiopharmaceutical development research space consists of 2 large (750 sq. ft. each) and 2 smaller laboratories (500 sq. ft. each), all with fume hoods. A positive pressure "clean room" with 2 vertical laminar flow benches (1 recirculating, 1 exhaust) is available for final preparation of labeled materials before administration to patients.

2. Cyclotron Complex

The Oak Ridge National Laboratory's 86-inch cyclotron accelerates protons to an energy of 22 MeV; internal beam intensities up to 3000  $\mu$ A are available. It has 8-inch wide dees and 4-inch dee-to-dee and dee-to-ground spacing and operates at 9,000 oersteds at a frequency of 13.4 Mc/sec. Three 20-inch oil diffusion pumps provide high pumping speed, moving 15,000 liters/sec at the operating pressure of  $3 \times 10^{-6}$  torr. An alteration to the 86-inch cyclotron which will permit rapid, remote changing of targets is to be installed in the spring of 1981; this should result in greater cyclotron availability. A hot cell is located approximately 50 ft. from the cyclotron. This hot cell has power-assisted manipulators and a hoist on an overhead rail which can be maneuvered over most of the cell area.

3. Animal Facilities

Adequate space is available for housing of animals on the 3rd floor of the existing Medical and Health Sciences Division building on Vance Road. The facility is accredited by the American Association for Accreditation of Laboratory Animal Care, and care of the animals is under the supervision of a veterinarian, Dr. Conrad B. Richter. Established standards of laboratory animal care, promulgated by the DHEW [Publication No. (NIH) 72-73] will be observed.

1079397

Research Plan: Facilities Available (continued)4. Clinical Studies

Clinical tests will be carried out at the Oak Ridge Associated Universities Medical and Health Sciences Division facilities in Oak Ridge. The patients will come from referring physicians at the Oak Ridge Hospital, the Knoxville hospitals, and other nearby institutions such as Vanderbilt University and the Veterans Administration Hospital in Nashville. The Medical and Health Sciences Division has a long history of cooperation with referring physicians and demonstrated ability to attract patients for experimental work. All proposed clinical studies will receive prior approval from the ORAU Human Studies Committee and the U.S. Food and Drug Administration before they are carried out in patients. Informed consent will be obtained for each study.

5. Equipment

## a. Nuclear medical instrumentation

- (1) ORTEC ECAT-I whole body positron emission computerized tomograph which will be upgraded to an ECAT II version (delivery and acceptance testing to require approximately 4-5 months from date of order).
- (2) Pho/Gamma V scintillation camera.
- (3) Ohio Nuclear dual-head rectilinear scanner modified for coincidence detection.
- (4) Associated equipment for monitoring and administering radio-pharmaceuticals.

## b. Other equipment

- (1) Two HPLC chromatographs.
- (2) HPLC refractive index and variable wavelength UV detectors.
- (3) HPLC gradient generator and strip chart recorder with computing integrator.
- (4) Four peristaltic pumps and fraction collectors with UV monitors and recorders.
- (5) Data Trac.
- (6) Packard liquid scintillation counter.
- (7) Packard refrigerated automatic gamma-scintillation counter.
- (8) Cary Model 14 recording spectrophotometer.

6. Oak Ridge Scientific Community

The surrounding scientific institutions employ many individuals who are now and can in the future be helpful in a variety of ways. Of these the Nuclear Medicine Technology Group at the Oak Ridge National Laboratory is the closest at hand and the University of Tennessee with its various disciplines and departments as well as the Memorial Research Center is nearby in Knoxville. A variety of basic and clinical disciplines are represented at the Medical and Health Sciences Division itself, i.e., pathology, cytogenetics, radiobiology, ultrastructural anatomy, biochemistry, and immunology.

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Research Plan: Facilities Available (continued)Use of Department of Energy (DOE) Facilities and DOE Contract Requirements

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

It is believed that in large measure the requirements of the DOE contract parallel conditions which NIH ordinarily applies to its grants. In the event of differences between NIH grant terms and the DOE 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 DOE for direct resolution with NIH.

By way of general information, ORAU's contract with the DOE is a cost-type contract financed under a Government-fund account. The specific contract work is formulated in cooperation with the DOE and authorized within general guidelines in the contract. Contract terms include DOE responsibilities for Government ownership and control of inventions, data, and other research products. Ownership of all equipment and facilities acquired by ORAU with DOE 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.

F. Collaborative Arrangements

The radiopharmaceutical development/nuclear medicine programs of the Oak Ridge Associated Universities Medical and Health Sciences Division have a long-standing collaborative arrangement with Oak Ridge National Laboratory, particularly the Nuclear Medicine Technology group (Health and Safety Research Division) and the staff associated with the 86-inch Cyclotron (Operations Division). These collaborative ties will be very important in the proposed project.

Mr. A. P. Callahan of the Nuclear Medicine Technology group will be a consultant to the project and will be involved in hot cell operation and general consultation in the area of radioactive syntheses. The 86-inch Cyclotron and associated hot cell facilities are to be made available for production of the  $^{11}\text{C}$ -labeled amino acids which will be used in the proposed studies.

Dr. Paul King of the Department of Biomedical Engineering, Vanderbilt University, Nashville, Tennessee, will also be a consultant to the project. Dr. King has a high level of expertise in the area of software development for improved computer applications with the ECAT positron tomographic scanner.

Dr. George Digenis of the School of Pharmacy, University of Kentucky, Lexington, Kentucky, has collaborated with us on the enzymatic resolution of  $^{11}\text{C}$ -

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NAME (last, first, middle initial)

Hübner, Karl F.

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Research Plan: Collaborative Arrangements (continued)

labeled amino acid racemates. He will be a consultant in the proposed resolution studies.

Drs. I. R. Collmann and S. Krauss of University of Tennessee Memorial Research Center and Hospital, Knoxville, Tennessee, G. Avant of Vanderbilt University Hospital and G. D. Dunn of the Veterans Administration Hospital, Nashville, Tennessee, are oncologists and gastroenterologists who will refer patients for the proposed studies and consult with the principal investigator on the clinical protocols to be followed and the interpretation of the clinical data.

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."

March 21, 1980

Date

Karl F. Hübner, M.D.

Karl F. Hübner, M.D.  
Principal Investigator"

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## H. APPENDIX

- A. Reprint of reference 16 (Washburn, L.C., Sun, T.T., Byrd, B.L., et al. High-level production of C-11-carboxyl-labeled amino acids. In Radiopharmaceuticals II, Proceedings of 2nd International Symposium on Radiopharmaceuticals, Seattle, Wash., 1979, pp. 767-777).
- B. Examples of clinical studies.
- C. Letter from Dr. Lee C. Washburn to Dr. Bernard Lefebvre inquiring about the availability of a chiral hydrophilic gel for resolution of amino acid racemates by high pressure liquid chromatography.
- D. Reply to above letter (Appendix C).
- E. Letter from Dr. G. D. Dunn, VA Hospital, Nashville, Tennessee, assuring referral of patients for clinical investigations.

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15. Hayes, R.L., Washburn, L.C., Wieland, B.W., et al. Synthesis and purification of  $^{11}\text{C}$ -carboxyl-labeled amino acids. *Int. J. Appl. Radiat. Isot.* 29:186-187, 1978.
16. Washburn, L.C., Sun, T.T., Byrd, B.L., et al. High-level production of C- $^{11}$ -carboxyl-labeled amino acids. In *Radiopharmaceuticals II, Proceedings of 2nd International Symposium on Radiopharmaceuticals, Seattle, Wash., 1979*, pp. 767-777.
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FEB 25 1980

W. H. Durr, Director, Office of Health and Environmental Research,  
EV-30, Mail Station E-291, Germantown, Maryland

ORAU GRANT APPLICATION ENTITLED 'C-11-AMINO ACIDS/POSITRON ECT FOR  
PANCREATIC STUDIES' (DOE NO. 24-81-80)

Enclosed for your review and approval is a copy of a new draft grant  
application to NIH entitled 'C-11-Amino Acids/Positron ECT for  
Pancreatic Studies' prepared by ORAU. Dr. Karl F. Hubner will be  
the principal investigator on the project. NIP funding in the  
amount of \$475,425 for direct costs for a three-year period  
(December 1, 1980 through November 30, 1983) is requested.  
\$235,675 is requested for direct costs for the first year.

All support will consist of the use of equipment and facilities  
assigned to the ORAU Medical and Health Sciences Division without  
charge. Please advise whether you approve joint DOE support of  
this project based on DOE's programmatic interest.

APPROVED BY  
K. M. HAYTHORN

K. M. Haythorn, Director  
Energy Programs and Support Division

69-10458-

Enclosure: *NFR*  
Grant Application

cc w/enc: *GW*  
John DeJoy, EV-410, HA, MS E-291, GTL

CONCURRENCES
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DATE 2-22-80
RTG SYMBOL ER-13 Bibb
INITIALS SIG <i>WJ</i>
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RTG SYMBOL ER-11 Haythorn
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*John DeJoy*

Oak Ridge  
Associated  
Universities

February 15, 1980

Mr. Kenneth M. Haythorn, Director  
Energy Programs and Support Division  
Department of Energy  
Oak Ridge, Tennessee 37830

Subject: DRAFT APPLICATION FOR A NEW GRANT ENTITLED *C-11-AMINO ACIDS/  
POSITRON ECT FOR PANCREATIC STUDIES*

Dear Mr. Haythorn:

Enclosed are four copies of a new grant application entitled *C-11-Amino Acids/Positron ECT for Pancreatic Studies*. This project will be under the direction of Dr. Karl F. Hübner and, if approved, will be carried out under procedures and policies already established between ORAU and the DOE for work in facilities owned by DOE. Should any questions arise during your review of this proposal please do not hesitate to call Dr. Hübner at 6-3098.

Formal copies of this application should be forwarded to NIH no later than March 26, 1980.

Sincerely,



Philip L. Johnson  
Executive Director

RYAN:br

Enclosures

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## SECTION I

Form Approved  
O.M.B. 68-R0249DEPARTMENT OF  
HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE

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## GRANT APPLICATION

TYPE	PROGRAM	NUMBER
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)

C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES

2. PRINCIPAL INVESTIGATOR

2A. NAME (Last, First, Initial)

Hubner, Karl F.

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

FROM

12/1/80

THROUGH

11/30/83

2B. TITLE OF POSITION

Chief Clinician, Medical and Health  
Sciences Division4. TOTAL DIRECT COSTS RE-  
QUESTED FOR PERIOD IN  
ITEM 3

\$475,425

5. DIRECT COSTS REQUESTED  
FOR FIRST 12-MONTH PERIOD

\$225,675

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

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

6. PERFORMANCE SITE(S) (See Instructions)

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

2D. DEGREE

M.D.

2E. SOCIAL SECURITY NO.

2F. TELE-  
PHONE  
DATAArea Code  
615TELEPHONE NUMBER AND EXTENSION  
576-30982G. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT  
(See Instructions)

Nuclear Medicine

2H. MAJOR SUBDIVISION (See Instructions)

Medical and Health Sciences Division

7. Research Involving Human Subjects (See Instructions)

A.  NO B.  YES Approved: \_\_\_\_\_C.  YES - Pending Review

Date

8. Inventions (Renewal Applicants Only - See Instructions)

A.  NO B.  YES - Not previously reportedC.  YES - Previously reported

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  
IRS No. 62-0476816  
Congressional District No. 3

11. TYPE OF ORGANIZATION (Check applicable item)

 FEDERAL  STATE  LOCAL  OTHER (Specify)  
Private Corporation, Non-Profit10. NAME, TITLE, AND TELEPHONE NUMBER OF OFFICIAL(S)  
SIGNING FOR APPLICANT ORGANIZATION(S)Dr. Philip L. Johnson  
Executive Director  
Oak Ridge Associated Universities  
P. O. Box 117  
Oak Ridge, TN  
Telephone Number (s) (615) 576-330012. NAME, TITLE, ADDRESS, AND TELEPHONE NUMBER OF  
OFFICIAL IN BUSINESS OFFICE WHO SHOULD ALSO BE  
NOTIFIED IF AN AWARD IS MADEW. F. Countiss  
Head, Office of Fiscal Services  
Oak Ridge Associated Universities  
P. O. Box 117  
Oak Ridge, TN 37830  
Telephone Number (615) 576-305613. IDENTIFY ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT  
FOR INSTITUTIONAL GRANT PURPOSES (See Instructions)

Other (Medical and Health Sciences Division)

14. ENTITY NUMBER (Formerly PHS Account Number)

1620476816A

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

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## SECTION 1

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE

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PROJECT NUMBER

## RESEARCH OBJECTIVES

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

Karl F. Hubner

Chief Clinician, Medical and Health Sciences  
Division (M&HSD)

Lee C. Washburn

Scientist, M&amp;HSD

Raymond L. Hayes

Chief Scientist, M&amp;HSD

Paul H. King

Associate Professor, Dept. of Biomedical  
Engineering, Vanderbilt University

TITLE OF PROJECT

C-11-AMINO ACIDS/POSITRON ECT FOR PANCREATIC STUDIES

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

Cancer of the pancreas is one of the leading causes of death among cancer patients. This can be attributed in part to the fact that a definitive diagnosis is usually made only at an advanced stage of the disease. We have shown, using positron emission computerized tomography (positron ECT) that <sup>11</sup>C-labeled DL-tryptophan and valine have high preferential uptakes in normal pancreatic tissue. Since the L-isomers of these two amino acids have an affinity for normal pancreas while the D-isomers tend to be preferentially taken up by tumor tissue, approximately the same <sup>11</sup>C concentrations occur in both normal and malignant pancreatic tissues with the DL mixture. We propose to develop rapid methods for the separation of the L-isomers of tryptophan and valine from their <sup>11</sup>C-labeled racemates. Using these agents pancreatic cancer would then be detected as zones of decreased or absent <sup>11</sup>C concentrations in the pancreas in the three-dimensional cross-sectional images obtained with positron ECT. Confirmation of the presence of a malignant lesion(s) would then be made with <sup>11</sup>C-labeled 1-aminocyclopentanecarboxylic acid or its cyclobutane analog, radiopharmaceuticals which we have shown to have no affinity for inflammatory lesions and to be effective tumor-localizing agents. This diagnostic protocol should thus provide a non-invasive method for the differential diagnosis of pancreatic disease. We also propose to use positron ECT to quantitatively measure the effect of therapy on the extraction/ utilization of amino acids by pancreatic neoplasms as a possible method of metabolically gauging individual responses to treatment.

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BUDGET ESTIMATE FOR ALL YEARS OF SUPPORT REQUEST FROM PUBLIC HEALTH SERVICE							
DIRECT COSTS ONLY (Omit Cents)							
DESCRIPTION	1ST PERIOD IS SAME AS DE TAILED BUDGET	ADDITIONAL YEARS SUPPORT REQUESTED (This application only)					
		2ND YEAR	3RD YEAR	4TH YEAR	5TH YEAR	6TH YEAR	7TH YEAR
PERSONNEL COSTS	61,125	65,250	69,800				
CONSULTANT COSTS (Include fees, travel, etc.)	3,600	7,200	3,600				
EQUIPMENT	121,000	0	0				
SUPPLIES	4,150	4,800	4,500				
TRAVEL	DOMESTIC	2,300	3,700	2,600			
	FOREIGN						
PATIENT COSTS	1,500	3,300	2,800				
ALTERATIONS AND RENOVATIONS							
OTHER EXPENSES	32,000	43,000	39,200				
TOTAL DIRECT COSTS	225,675	127,250	122,500				
TOTAL FOR ENTIRE PROPOSED PROJECT PERIOD (Enter on Page 1, Item 4) →					\$ 475,425		
<p>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.)</p> <p>Recurring increases in personnel costs computed at 7% average.</p> <p><u>2nd Year Cost Increase Justification:</u> Increases in consultant costs, patient transportation costs and other costs (primarily cyclotron usage) for the second year are a result of increasing the number of patients studied. Some patients will be studied during the first year, but a large portion of the year will be spent upgrading the ECAT and related pharmacological systems. The second year will involve larger numbers of patients thus increasing funds spent for Dr. Paul King, transportation of patients and additional cyclotron runs.</p> <p><u>Equipment Justification</u></p> <p>Our experience with the ORTEC ECAT I scanning system using phantoms has indicated to us that this system, while producing images of diagnostic quality, does not yield data which are amenable to quantitation. We propose, therefore, to upgrade our instrument to an ECAT II system so that a major contributing factor, accidental coincidences ("randoms") may be eliminated. Another major advantage of the ECAT II system is the fact that simultaneous image reconstruction cojoint with image acquisition can be made; this will permit scanning to proceed while reconstruction of the previous scan is in process, thus greatly improving the efficiency of the system. When the present ECAT I is upgraded to an ECAT II version, this equipment will have</p>							

## 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 Karl F. Hübner	TITLE Director, Outpatient Nuclear Medicine	BIRTHDATE (Mo., Day, Yr.) [REDACTED]	
PLACE OF BIRTH (City, State, Country) [REDACTED] Germany	PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date) USA	SEX <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female	
EDUCATION (Begin with baccalaureate training and include postdoctoral)			
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HONORS [REDACTED]			
MAJOR RESEARCH INTEREST Nuclear Medicine Radiation Biology and Medicine	ROLE IN PROPOSED PROJECT Principal Investigator - Clinician	Environment Information	
RESEARCH SUPPORT (See instructions)			

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.)

1977 - Present Director, Radiation Emergency Assistance Center/Training Site, Oak Ridge Associated Universities, Oak Ridge, TN.

1975 - Present Director, Outpatient Nuclear Medicine, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.

1973 - 1974 Senior Research Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.

1971 - 10/73 Senior Staff Member with Clinical Staff, Medical Division, Oak Ridge Associated Universities, Oak Ridge, TN.

1967 - 1970 Research Associate in Experimental Immunology, Medical Division, Oak Ridge Associated Universities, Oak Ridge, TN.

1964 - 1967 Resident in Pediatrics, University of Tübingen, Medical School, Germany.

1962 - 1964 Resident in Clinical Investigation, Medical Division, Oak Ridge Institute of Nuclear Studies (now Oak Ridge Associated Universities), Oak Ridge, TN.

1960 - 1961 Internship (rotating) at 2nd General Hospital of the U.S. Army, and at the 86th Tactical Hospital of the U.S. Air Force, Germany.

Publications:

Ricks, R.C., Beck, J., Berger, J., and Hübner, K.F. Responder's Guidebook for Radioactive Materials Transportation Incidents, 1979, U.S. Department of Transportation (DOT/RSPA/MTB-79/8). (In press)

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Hubner, Karl F.

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Publications: (Karl F. Hübner)

Partain, C.L., Hübner, K.F., Stabb, E.V., Scatliff, J.H., Miller, G.F., and Gibbs, W.D. CSF kinetics: comparison of nuclear medicine, contrast enhanced CT, and positron emission tomography. *Investigative Radiology* 14(5):377, Sept.-Oct., 1979 (abstract).

Buonocore, E., and Hübner, K.F. Comparison of positron emission computer assisted transaxial tomography (ECT) with transmission CT and ultrasonography for the diagnosis of pancreatic disease. Presented at the Eastern Radiological Society, Mid Pines, North Carolina, April, 1979 (abstract).

Hübner, K.F., Buonocore, E., Gibbs, W.D., Holloway, S., and Byrd, B.L. Differentiation of pancreatic and other retroperitoneal tumors by positron emission computerized tomography (ECT). *J. Nucl. Med.* 20:631, 1979.

Hübner, K.F., Andrews, G.A., Washburn, L., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Winebrenner, J.D. Tumor location with 1-aminocyclopentane [<sup>11</sup>C]-carboxylic acid: preliminary clinical trials with single-photon detection. In *Year Book of Cancer*, R.L. Clark, R.W. Cumley and R.C. Hickey, eds., Year Book Medical Publishers, Inc., Chicago, 1979, pp. 237-239.

Hübner, K.F., and Buonocore, E. Emission computerized tomography (ECT) with <sup>11</sup>C-labeled amino acids, transmission CT and ultrasonography (US) in the diagnosis of pancreatic disease. Presented at the Sixth International Congress of Radiation Research, Tokyo, Japan, 1979 (abstract).

Hübner, K.F., Andrews, G.A., Buonocore, E., Hayes, R.L., Washburn, L.C., Collmann, I.R., and Gibbs, W.D. Carbon-11-labeled amino acids for the rectilinear and positron tomographic imaging of the human pancreas. *J. Nucl. Med.* 20:507-513, 1979.

Buonocore, E., Hübner, K.F., and Collmann, I.R. Differentiation of retroperitoneal tumor using positron emission computed tomography. *J. Comput. Asst. Tomogr.* 3(6): 825-828, 1979.

Buonocore, E., and Hübner, K.F. Positron-emission computed tomography of the pancreas: a preliminary study. *Radiology* 133:195-201, 1979.

Buonocore, E., and Hübner, K.F. Comparison of positron emission computer assisted transaxial tomography (ECT) with transmission CT and ultrasonography for the diagnosis of pancreatic disease. Presented at the Annual meeting of the Radiological Society of North America, Chicago, Illinois, 1978 (abstract).

Sauerbrunn, B.J.L., Andrews, G.A., and Hübner, K.F. <sup>67</sup>Ga-citrate imaging in genitourinary tract tumors: report of cooperative study. *J. Nucl. Med.* 19:470-475, 1978.

Lushbaugh, C.C., Hubner, K.F., and Ricks, R.C. Medical aspects of nuclear radiation emergencies. *Emergency* 10:32-35, 1978.

Lawless, D., Brown, D.H., Hubner, K.F., Colyer, S.P., Carlton, J.E., and Hayes, R.L. Isolation and partial characterization of a <sup>67</sup>Ga-binding glycoprotein from Morris 5123C rat hepatoma. *Can. Res.* 38:4440-4444, 1978.

Hubner, K.F., Hayes, R.L., Washburn, L.C., Gibbs, W.D., Byrd, B.L., and Butler, T.A. Scanning of the human pancreas with DL-valine-1-<sup>11</sup>C and DL-tryptophan-1-<sup>11</sup>C. *J. Nucl. Med.* 19:686, 1978 (abstract).

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Hubner, Karl F.

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Publications: (Karl F. Hübner, continued)

Hubner, K.F., Andrews, G.A., Gibbs, W.D., Holloway, S., Hayes, R.L., and Washburn, L.C. Initial diagnostic results with  $^{11}\text{C}$ -labeled amino acids and the emission positron tomograph. In Proceedings of the Second World Federation of Nuclear Medicine and Biology, p. 13 (abstract), Washington, D.C., 1978.

Andrews, G.A., Hubner, K.F., and Greenlaw, R.H. Gallium-67 citrate imaging in malignant lymphoma: final report of cooperative group. J. Nucl. Med. 19:1013-19, 1978.

Johnston, G.S., Go, M.F., Benua, R.S., Larson, S.M., Andrews, G.A., and Hubner, K.F.  $^{67}\text{Ga}$ -citrate imaging in Hodgkin's disease: final report of cooperative group. J. Nucl. Med. 18:692-698, 1977.

Hubner, K.F., Andrews, G.A., Washburn, L., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Winebrenner, J.D. Tumor location with 1-aminocyclopentane [ $^{11}\text{C}$ ]-carboxylic acid: preliminary clinical trials with single-photon detection. J. Nucl. Med. 18:1215-1221, 1977.

Hubner, K.F., Andrews, G.A., Lushbaugh, C.C., and Tompkins, E. A follow-up study program for persons irradiated in radiation accidents. In Handling of Radiation Accidents 1977, Proceedings of a Symposium, pp. 57-70. Vienna, Austria: International Atomic Energy Agency, 1977.

Hubner, K.F., Andrews, G.A., Hayes, R.L., Poggenburg, J.K., and Solomon, A. The use of rare earth radionuclides and other bone-seekers in evaluating bone lesions in patients with multiple myeloma and solitary plasmacytoma. Radiology 125:171-176, October, 1977.

Andrews, G.A., Hubner, K.F., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Collmann, I.R. Clinical studies of  $^{11}\text{C}$ -labeled amino acids. J. Nucl. Med. 18:638, 1977 (Poster Session, abstract).

Andrews, G.A., Hubner, K.F., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., and Butler, T.A. Clinical tumor scanning with  $^{11}\text{C}$ -carboxyl-labeled 1-aminocyclopentanecarboxylic acid ( $^{11}\text{C}$ -ACPC). Presented at the 17th Annual Southeastern Chapter of the Society of Nuclear Medicine, Louisville, Kentucky, 1976 (abstract).

Hubner, K.F. and Littlefield, L.G. Burkitt's lymphoma in three American children. Clinical and cytogenetic observations. Am. J. Dis. Child. 129:1219-1223, Oct., 1975.

Swartzendruber, D.C. and Hubner, K.F. Effect of external whole-body X-irradiation on gallium-67 retention in mouse tissues. Radiat. Res. 55:457-468, 1973.

Gengozian, N., Edwards, C.L., Vodopick, H.A., and Hubner, K.F. Bone marrow transplantation in a leukemic patient following immunosuppression with antithymocyte globulin and total body irradiation. Transplantation 15:446-454, 1973.

Gengozian, N. and Hubner, K.F. "In situ" visualization of a graft-vs-host reaction. J. Immunol. 106:1159-1165, 1971.

Hubner, K. and Brown, D.W. Scanning of the spinal subarachnoid space after intrathecal injection of  $^{131}\text{I}$  labeled human serum albumin. J. Nucl. Med. 6:465-472, 1965.

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DO NOT TYPE IN THIS SPACE-BINDING MARGIN

## 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 Lee C. Washburn	TITLE Scientist	BIRTHDATE (Mo., Day, Yr.) [REDACTED]	
PLACE OF BIRTH (City, State, Country) [REDACTED] Kentucky, USA	PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date) USA	SEX <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female	
EDUCATION (Begin with baccalaureate training and include postdoctoral)			
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HONORS [REDACTED]			
MAJOR RESEARCH INTEREST Radiopharmaceutical development	ROLE IN PROPOSED PROJECT Resolution of $^{11}\text{C}$ -labeled amino acids and production of these agents for clinical use.		
RESEARCH SUPPORT (See instructions)			

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.)

- April 1974 - present Scientist, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.  
 June 1972 - March 1974 Presidential Intern, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN.  
 March-June 1972 Research Associate, Vanderbilt University, Nashville, TN.

Publications:

Jay, M., Digenis, G.A., Chaney, J.E., Washburn, L.C., Byrd, B.L., Hayes, R.L., and Callahan, A.P. Synthesis and brain uptake of carbon-11 phenethylamine. (Submitted for publication)

Blank, M.L., Cress, E.A., Byrd, B.L., Washburn, L.C., and Snyder, F. Liposomal encapsulated Zn-DTPA for removing intracellular heavy metals. (Submitted for publication)

Digenis, G.A., Casey, D.L., Wesner, D.A., Washburn, L.C., and Hayes, R.L. Preparation of optically active C-11-amino acids. J. Nucl. Med. 20:662, 1979 (abstract).

Hubner, K.F., Andrews, G.A., Buonocore, E., Hayes, R.L., Washburn, L.C., Collmann, I.R., and Gibbs, Wm.D. Carbon-11-labeled amino acids for the rectilinear and positron tomographic imaging of the human pancreas. J. Nucl. Med. 20:507-513, 1979.

Continuation page

Publications: (Lee C. Washburn)

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. [Carboxyl-<sup>11</sup>C] l-Aminocyclobutanecarboxylic acid, a potential agent for tumor localization. J. Nucl. Med. 20:1055-1061, 1979.

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. DL-[Carboxyl-<sup>11</sup>C] tryptophan, a potential agent for pancreatic imaging: production and preclinical investigations. J. Nucl. Med. 20:857-864, 1979.

Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., Butler, T.A., and Callahan, A.P. High-Level production of C-<sup>11</sup>-carboxyl-labeled amino acids. In Radiopharmaceuticals II, proceedings of 2nd International Symposium on Radiopharmaceuticals, Seattle, Wash., 1979, pp. 767-777.

Lushbaugh, C.C. and Washburn, L.C. FDA IND Approval for Zn-DTPA, new clinical agent for decorporation therapy of actinides. J. Nucl. Med. 20:73, 1979.

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Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. Further pre-clinical studies of C-<sup>11</sup>-DL-tryptophan, a potential pancreas-imaging agent. In Proc. of the 2nd International Congress of the World Federation of Nuclear Medicine and Biology, Washington, D.C., September 17-21, 1978, p. 41.

Hayes, R.L., Washburn, L.C., Wieland, B.W., Sun, T.T., Turtle, R.R., and Butler, T.A. Carboxyl-labeled <sup>11</sup>C-l-aminocyclopentanecarboxylic acid, a potential agent for cancer detection. Year Book of Cancer 1978, pp. 236-237.

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Washburn, L.C. and Hayes, R.L. Importance of excess base in the synthesis of sodium phosphorothioate. In Inorganic Syntheses, Vol. 17, A. G. MacDiarmid, ed., McGraw-Hill Book Co., 1978, pp. 193-194.

Washburn, L.C., Sun, T.T., Anon, J.B., and Hayes, R.L. Effect of structural modifications on the tumor specificity of alicyclic  $\alpha$ -amino acids. In Proc. of the 18th Annual Meeting of the Southeastern Chapter, Society of Nuclear Medicine, Part 2, Winston-Salem, N.C., October 12-15, 1977 (abstract).

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Hubner, Karl F.

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Publications: (Lee C. Washburn)

Hubner, K.F., Andrews, G.A., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Winebrenner, J.D. Tumor location with 1-aminocyclopentane [ $^{11}\text{C}$ ] carboxylic acid: preliminary clinical trials with single-photon detection. J. Nucl. Med. 18:1215-1221, 1977.

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Washburn, L.C., Sun, T.T., Rafter, J.J., and Hayes, R.L. C-11-Labeled amino acids for pancreas visualization. J. Nucl. Med. 17:557-558, 1976.

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Washburn, L.C., Coffey, J.L., Watson, E.E., Sun, T.T., and Hayes, R.L. Radiation dosimetry of some  $^{11}\text{C}$ -labeled amino acid pharmaceuticals. In Radiopharmaceutical Dosimetry Symposium, R.J. Cloutier, J.L. Coffey, W.S. Snyder, and E.E. Watson, eds., U. S. Dept. of Health, Education and Welfare, Washington, D.C., June 1976, pp. 441-451.

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Hayes, R.L., Rafter, J.J., Washburn, L.C., and Byrd, B.L. Affinity of  $^{253}\text{einsteinium}$  for tumor tissue. Nature New Biology 246:23-25, 1973.

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## BIOGRAPHICAL SKETCH

(Give the following information for all professional personnel listed on page 1, beginning with the Principal Investigator. Use continuation pages and follow the same general format for each person.)

NAME Raymond L. Hayes		TITLE Chief Scientist		BIRTHDATE (Mo., Day, Yr.) [REDACTED]
PLACE OF BIRTH (City, State, Country) [REDACTED], Arizona USA		PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date) USA		SEX <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female
EDUCATION (Begin with baccalaureate training and include postdoctoral)				
INSTITUTION AND LOCATION		DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]
HONORS [REDACTED]				
MAJOR RESEARCH INTEREST Radiopharmaceutical Development			ROLE IN PROPOSED PROJECT	
RESEARCH SUPPORT (See instructions)				

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.)

1950 - present Chief Scientist, Medical & Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, Tennessee.  
1944 Senior Chemist, U. S. Rubber Co., Charlotte, North Carolina.

Publications:

Hayes, R.L., Byrd, B.L., Rafter, J.J., and Carlton, J.E. The effect of scandium on the tissue distribution of Ga-67 in normal and tumor-bearing rodents. J. Nucl. Med. (in press).

Hayes, R.L., Szymendera, J.J., and Byrd, B.L. Effect of food intake on the tissue distribution of gallium-67: Concise communication. J. Nucl. Med. 20:938-940, 1979.

Digenis, G.A., Casey, D.L., Wesner, D.A., Washburn, L.C., and Hayes, R.L. Preparation of optically active C-11-amino acids. J. Nucl. Med. 20:662, 1979 (abstr.).

Brown, D.H., Carlton, J.E., Rafter, J.J., and Hayes, R.L. A large scale extraction procedure for the purification of a Ga-67 binding glycoprotein. J. Nucl. Med. 20:682, 1979 (abstr.).

Hayes, R.L., Rafter, J.J., and Byrd, B.L. Studies of the mechanism of gallium-67 uptake by tumor, abscess and normal tissues. J. Nucl. Med. 20:672-673, 1979 (abstr.).

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Publications: R. L. Hayes (continued)

- Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. [Carboxyl-<sup>11</sup>C] 1-Aminocyclobutanecarboxylic acid, a potential tumor-seeking agent. *J. Nucl. Med.* 20:1055-1061, 1979.
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- Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., Butler, T.A., and Callahan, A.P. High-Level production of C-11-carboxyl-labeled amino acids. *In Radiopharmaceuticals II, proceedings of 2nd International Symposium on Radiopharmaceuticals, Seattle, Wash., 1979, pp. 767-777.*
- Hubner, K.F., Andrews, G.A., Buonocore, E., Hayes, R.L., Washburn, L.C., Collmann, I.R., and Gibbs, W.D. Carbon-11-labeled amino acids for the rectilinear and positron tomographic imaging of the human pancreas. *J. Nucl. Med.* 20:507-513, 1979.
- Brown, D.H., Carlton, J.E., Rafter, J.J., and Hayes, R.L. Further purification of a small <sup>67</sup>Ga-binding particle found in Morris 5123C hepatomas. Presented at the Sixth Annual Meeting of Southeastern Cancer Research Association, Kiawah Island, S. Carolina, November 15-17, 1978.
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- Washburn, L.C., Sun, T.T., Byrd, B.L., Hayes, R.L., and Butler, T.A. Further pre-clinical studies of C-11-DL-tryptophan, a potential pancreas-imaging agent. *In Proc. of the 2nd International Congress of the World Federation of Nuclear Medicine and Biology, Washington, D.C., September 17-21, 1978, p. 41.*
- Kuniyasu, Y., Hayes, R.L., and Carlton, J.E. A Ga-68 albumin preparation for positron tomography of the liver. *In Proc. of the 2nd International Congress of the World Federation of Nuclear Medicine and Biology, Washington, D.C., September 17-21, 1978, p. 90.*
- Hayes, R.L., Byrd, B.L., and Szymendera, J. Effect of food intake on the tissue distribution of gallium-67. *In Proc. of the 2nd International Congress of the World Federation of Nuclear Medicine and Biology, Washington, D.C., September 17-21, 1978, p. 112.*
- Lawless, D., Brown, D.H., Hubner, K.F., Colyer, S.P., Carlton, J.E., and Hayes, R.L. Isolation and partial characterization of a <sup>67</sup>Ga-binding glycoprotein from a rat hepatoma. *Cancer Res.* 38:4440-4444, 1978.
- Hayes, R.L. Chemistry and radiochemistry of metal-ion nuclides commonly employed in radiopharmaceuticals. *In The Chemistry of Radiopharmaceuticals, N.D. Heindel, H.D. Burns, T. Honda, and L.W. Brady, eds. Masson Publishing, N.Y., 1978, pp.155-167.*
- Hayes, R.L. The medical use of gallium radionuclides: a brief history with some comments. *Semin. Nucl. Med.* 8:183-191, 1978.

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Publications: R. L. Hayes (continued)

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Hayes, R.L., Washburn, L.C., Wieland, B.W., Sun, T.T., Turtle, R.R., and Butler, T.A. Carboxyl-labeled  $^{11}\text{C}$ -1-aminocyclopentanecarboxylic acid, a potential agent for cancer detection. *Year Book of Cancer* 1978, pp. 236-237.

Hayes, R.L., Washburn, L.C., Wieland, B.W., Sun, T.T., Anon, J.B., Butler, T.A., and Callahan, A.P. Synthesis and purification of  $^{11}\text{C}$ -carboxyl-labeled amino acids. *Int. J. Appl. Radiat. Isotopes* 29:186-187, 1978.

Washburn, L.C., Wieland, B.W., Sun, T.T., Hayes, R.L., and Butler, T.A. [ $^{11}\text{C}$ ] DL-Valine, a potential pancreas-imaging agent. *J. Nucl. Med.* 19:77-83, 1978.

Washburn, L.C., Sun, T.T., Anon, J.B., and Hayes, R.L. Effect of structural modifications on the tumor specificity of alicyclic  $\alpha$ -amino acids. *In Proc. of 18th Annual Meeting of Southeastern Chapter, Society of Nuclear Medicine, Part 2, Winston-Salem, N.C., October 12-15, 1977 (abstr.)*.

Hayes, R.L., Rafter, J.J., and Butler, T.A. Copper-64 as a possible positron tomographic agent for detection of cancer. *In Proc. of 18th Annual Meeting of Southeastern Chapter, Society of Nuclear Medicine, Part 2, Winston-Salem, N.C., October 12-15, 1977 (abstr.)*.

Hayes, R.L., Carlton, J.E., and Kuniyasu, Y. A Ga-68 albumin preparation for positron tomography of the liver. *In Proc. of 18th Annual Meeting of Southeastern Chapter, Society of Nuclear Medicine, Part 2, Winston-Salem, N.C., October 12-15, 1977 (abstr.)*.

Hayes, R.L. The tissue distribution of gallium radionuclides. *J. Nucl. Med.* 18:740-742, 1977.

Hubner, K.F., Andrews, G.A., Hayes, R.L., Poggenburg, J.K. Jr., and Solomon, A. The use of rare-earth radionuclides and other bone-seekers in the evaluation of bone lesions in patients with multiple myeloma or solitary plasmacytoma. *Radiology* 125(1):171-176, 1977.

Hubner, K.F., Andrews, G.A., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Winebrenner, J.D. Tumor location with 1-aminocyclopentane [ $^{11}\text{C}$ ] carboxylic acid: preliminary clinical trials with single-photon detection. *J. Nucl. Med.* 18:1215-1221, 1977.

Andrews, G.A., Hubner, K.F., Washburn, L.C., Wieland, B.W., Gibbs, W.D., Hayes, R.L., Butler, T.A., and Collmann, I.R. Clinical studies of C-11-labeled amino acids. *J. Nucl. Med.* 18:638, 1977 (abstr.).

Washburn, L.C., Wieland, B.W., Sun, T.T., and Hayes, R.L.  $^{11}\text{C}$ -Labeled amino acids as agents for tumor and pancreas visualization. *J. Labeled Compds. Radiopharmaceuticals* 13:203, 1977.

Wieland, B.W., Washburn, L.C., Turtle, R.R., Hayes, R.L., and Butler, T.A. Development of cyclotron targetry and remote radiochemical techniques for the continuous large-scale production of  $^{11}\text{C}$ -labeled amino acids. *J. Labeled Compds. Radiopharmaceuticals* 13(2):202, 1977.

BIOGRAPHICAL SKET

(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 Paul Harvey King		TITLE		BIRTHDATE (M, Day, Yr.) [REDACTED]
PLACE OF BIRTH (City, State, Country) [REDACTED] Indiana, USA		PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date) USA		SEX <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female
EDUCATION (Begin with baccalaureate training and include postdoctoral)				
INSTITUTION AND LOCATION		DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]
HONORS [REDACTED]				
MAJOR RESEARCH INTEREST Biomedical Engineering		ROLE IN PROPOSED PROJECT		
RESEARCH SUPPORT (See instructions)				

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.)

July 1978 - July 1979 Sabbatical - Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, TN. (Presently a consultant).  
 1972 - present Associate Professor, Vanderbilt University, Nashville, TN.  
 Feb. 1971 - present Vanderbilt and Veterans Hospitals, Vectorcardiography research.  
 Aug. 1969 - present Vanderbilt and Veterans Hospital, Dynamics of bone healing, gait analysis.  
 Feb. 1966 - present Nuclear Medicine Dept., Vanderbilt Hospital, Nashville, TN.  
 Dec. 1966 - Sept. 1969 Kidney Dialysis Unit, Veteran's Hospital, Nashville, TN.  
 Sept. 1962 - Sept. 1965 Highland View Hospital (Metabolic Ward), Cleveland, Ohio.  
 June 1962 - Sept. 1962 Bell Aerosystems Co., (accelerometer research and design), Cleveland, Ohio.  
 June 1961 - June 1962 Case Institute of Technology (Asst. in Accelerometer Research), Cleveland, Ohio.

Publications:

Wieland, B.W., Highfill, R.R., and King, P.H. Proton accelerator targets for the production of <sup>11</sup>C, <sup>13</sup>N, <sup>15</sup>O, and <sup>18</sup>F. IEEE Transactions on Nuclear Sciences, Vol. NS-26(1):1713-1717, 1979.

Pickens, D.R., King, P.H., Patton, J.A., and Brill, A.B. The design, construction, and preliminary testing of a mutually orthogonal coincident focal point tomographic scanner, In Proc. of 13th Annual Meeting, Association for the Advancement of Medical

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Publications: P. H. King (continued)

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Smith, R.F., Stanton, K., Stoop, D., Brown, D., and King, P.H. Quantitative electrocardiography during extended spaceflight. Basic Environmental Problems of Man in Space, Ashton Grayziel, ed., Pergamon Press, 1976, pp. 89-102.

Smith, R.F., Stanton, K., Stoop, D., Janusz, W., and King, P.H. Quantitative electrocardiography during extended spaceflight: The second skylab mission. Aviation, Space and Environmental Medicine, April 1976, pp. 353-359.

Smith, R.F., King, P.H., Stanton, K., Stoop, D., and Brown, D. Quantitative electrocardiography during extended spaceflight. The first skylab mission. Astronautica Acta 2:89-102, 1975.

Patton, J.A., Brill, A.B., and King, P.H. A new mode of collection and display of three dimensional data for static and dynamic radiotracer studies. Proceedings of Symposium on Medical Radioisotope Scintigraphy 1972, Vol. 1, IAEA, Vienna, 1973, pp. 355-368.

Patton, J., Brill, A.B., and King, P.H. Transverse section brain scanning with multicrystal cylindrical imaging device. Conference on Radionuclide Tomography, Sept. 15, Tomographic Imaging in Nuclear Medicine. Society of Nuclear Medicine, New York, 1973, pp. 28-43.

King, P.H., Brill, A.B., Patton, J.A., Pickens, D.R., and Sweeney, J. Design of a new tomographic scanner. Conference on Computer Applications in Biomedical Instrumentation, June 6, 1972, at the University of Tennessee Space Institute, Tullahoma, Tennessee.

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King, P.H., Ginn, H.E., Baker, W.R., and Frost, A.B. Computer optimization of hemodialysis. In Conference on Computer Applications in Biomedical Instrumentation, June 5, 1972, at the University of Tennessee Space Institute, Tullahoma, Tennessee.

King, P.H., Patton, J., Pickens, D.R., Sweeney, J., and Brill, A.B. A multidetector orthogonally coincident focal point tomographic scanner. Sou. Med. J. 64(11):1422, 1971.

Brill, A.B., Johnston, R.E., Davies, H., King, P.H., Erickson, J., Williams, H., and Nash, R. Analysis of imaging techniques using digitally simulated scans. Sou. Med. J. 62, 1969.

Patton, J., Brill, A.B., Erickson, J., and King, P.H. Cylindrical array tomographic scanner with focusing collimators and its possible adaptation for fluorescence scanning of brain tumors. Sou. Med. J. 62:1434, 1969.

King, P.H., Ginn, H.E., Baker, W.R., Frost, A.B., and Matter, B.J. Computer optimization of urea dynamics during hemodialysis. Trans. Am. Soc. Artif. Int. Organs Vol. XIV, pp. 389-393, 1968.

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Hubner, Karl F.

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Publications: P. H. King (continued)

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Paul H. King has 34 other publications, abstracts and presentations.

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## 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 I. Reid Collmann	TITLE Clinical Professor of Medicine	BIRTHDATE (Mo., Day, Yr.) [REDACTED]	
PLACE OF BIRTH (City, State, Country) [REDACTED] Pennsylvania, U.S.A.	PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date) U.S.A.	SEX <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female	
EDUCATION (Begin with baccalaureate training and include postdoctoral)			
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HONORS [REDACTED]			
MAJOR RESEARCH INTEREST		ROLE IN PROPOSED PROJECT	
RESEARCH SUPPORT (See instructions)			

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.)

1966 - present Clinical Professor of Medicine, University of Tennessee Memorial Research Center & Hospital, Knoxville, Tennessee.  
 1965 - present Chief, Department of Gastroenterology, University of Tennessee Memorial Research Center & Hospital, Knoxville, Tennessee.  
 1954 - 1965 Captain, MC, U. S. Army, 2nd General U. S. Army Hospital, Lanstuhl, W. Germany.

Publications:

Hubner, K.F., Andrews, G.A., Buonocore, E., Hayes, R.L., Washburn, L.C., Collmann, I.R., and Gibbs, W.D. Carbon-11-Labeled amino acids for the rectilinear and positron tomographic imaging of the human pancreas. J. Nucl. Med. 20:507-513, 1979.

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E (Last, first, middle initial)
Hubner, Karl F.
SOCIAL SECURITY NUMBER
[REDACTED]

Continuation page

Publications: I. Reid Collmann (continued)

Lange, R.D., Chernoff, A.I., Jordan, T.A., and Collmann, I.R. Experience with a hemagglutination-inhibition test for carcinoembryonic antigen: preliminary report. In Proceedings of the First Conference and Workshop on Embryonic and Fetal Antigens in Cancer, N.G. Anderson and J. H. Coggin, Jr., eds., 1971, pp. 379-386.

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## BIOGRAPHICAL SKETCH

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

NAME George A. Digenis	TITLE Prof. of Medicinal Chemistry Assoc. Prof. Nuclear Medicine	BIRTHDATE (Mo., Day, Yr.) [REDACTED]	
PLACE OF BIRTH (City, State, Country) [REDACTED] Greece	PRESENT NATIONALITY (If non-U.S. citizen, indicate kind of visa and expiration date) US. Citizen	SEX <input checked="" type="checkbox"/> Male <input type="checkbox"/> Female	
EDUCATION (Begin with baccalaureate training and include postdoctoral)			
INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	SCIENTIFIC FIELD
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
HONORS [REDACTED]			
MAJOR RESEARCH INTEREST Organic and Medicinal Chemistry, Biorganic Mechanisms and Radiopharmaceuticals	ROLE IN PROPOSED PROJECT		
RESEARCH SUPPORT (See instructions)			

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.)

- 1974 - present Professor of Medicinal Chemistry and Associate Professor of Nuclear Medicine (1975-present) Colleges of Pharmacy and Medicine, University of Kentucky, Lexington, KY.
- 1976 - present Associate Scientist, Sloan Kettering Institute for Cancer Research, New York, N.Y.  
Director of Radiopharmacy Program, College of Pharmacy, University of Kentucky, Lexington, KY.

Publications:

McQuinn, R.L., Feola, J., and Digenis, G.A. The effect of vitamin A on the uptake of a water soluble and lipid soluble nitrosourea by the EMT6 mouse mammary tumor. Int. J. Rad. Oncology, Biol. Physics 5:1577, 1979.

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Continuation page:

Publications - George A. Digenis (continued)

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Continuation page

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NAME (last, first, middle initial)

Hudner, Karl F.

SOCIAL SECURITY NUMBER

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## RESEARCH PLAN

### A. Specific Aims

Our overall objective is to evaluate the potential of using  $^{11}\text{C}$ -labeled natural and unnatural amino acids in conjunction with positron emission computerized tomography for the non-invasive differential diagnosis of pancreatic disease.

In selected patients with suspected cancer of the pancreas, the uptake and distribution of  $^{11}\text{C}$ -labeled L-tryptophan or L-valine will be studied tomographically in order to determine whether in man the L-isomer localizes to a higher degree in normal pancreatic tissue than in neoplastic lesions of the pancreas, pancreatitis, pancreatic cysts, and benign tumors. (We have observed that DL-mixtures localize in both normal pancreas and in pancreatic carcinoma.) In order to use the L-form of  $^{11}\text{C}$ -labeled tryptophan or valine for clinical investigations, a method will have to be developed for resolving the DL-racemates of these  $^{11}\text{C}$ -labeled amino acids rapidly enough to be compatible with the short half-life of  $^{11}\text{C}$  (20.4 min). Both chromatographic and enzymatic procedures will be investigated.

These same patients will also be examined with either  $^{11}\text{C}$ -l-aminocyclopentane-carboxylic acid ( $^{11}\text{C}$ -ACPC) or  $^{11}\text{C}$ -l-aminocyclobutanecarboxylic acid ( $^{11}\text{C}$ -ACBC), alicyclic unnatural amino acids that we have identified as tumor-localizing agents. The choice will be based on a determination in man of the agent having the higher uptake in pancreatic tumors relative to that in normal pancreas. Therefore, this research will test the potential of using  $^{11}\text{C}$ -labeled L-tryptophan or L-valine in conjunction with  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC for the complete differential diagnosis of pancreatic disease by positron tomography.

A further aim of this proposed work is to develop and test methods for the quantitative analysis of the in vivo distribution of  $^{11}\text{C}$ -labeled natural and unnatural amino acids in normal pancreas and specific sites of pancreatic disease. We propose to measure quantitatively amino acid extraction by pancreatic neoplasms before, during, and after chemotherapy or radiation therapy, i.e., to develop a model system for objectively gauging response of pancreatic tumors to therapy based on metabolic parameters rather than standard radiographic or subjective clinical evaluations.

### B. Significance

Carcinoma of the pancreas is now the fourth leading cause of death among cancer patients (1). It is usually diagnosed at an advanced stage. Although not yet proven, it is reasonable to assume that the prognosis for patients with cancer of the pancreas could be improved through earlier diagnosis and treatment.

The development of computer-assisted tomography (CT) and ultrasound (US) have greatly improved the diagnostic assessment of pancreatic carcinoma, although the diagnostic accuracy is not better than 84% for CT and 80% for US, as was shown by Husband et al (2). Other US studies by Feinberg et al (3) gave accurate diagnostic information in 93.8% of the cases. Haaga et al (4) diagnosed pancreatic neoplasms with CT correctly in 28 of 32 cases whereas US was incorrect in 3 of 7 patients. The accuracy of US in diagnosing pancreatic carcinoma varies considerably from laboratory to laboratory, but nevertheless US seems to be quite helpful as a screening method.

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Washburn, Karl F.

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Research Plan: Significance (continued)

A nuclear medical technique employed with some success for diagnosis of pancreatic carcinoma involves imaging of the pancreas with a modified amino acid,  $^{75}\text{Se}$ -labeled L-selenomethionine. The pancreas is known to have a pronounced avidity for some amino acids (5). The use of a modified methionine is, however, not based on its avidity for pancreas so much as it is on the fact that methionine contains a sulfur atom which can be replaced by the gamma-emitting radionuclide  $^{75}\text{Se}$  without greatly altering the localization of the amino acid in the pancreas (6). With this technique cancers of the pancreas are seen as areas of decreased or absent uptake when the organ is visualized, usually by  $^{99\text{m}}\text{Tc}$ -colloid liver subtraction techniques (7). The procedure has been successful enough to become rather widely adopted, but it is far from ideal for several reasons: (1) the normal variability in the shape and position of the pancreas, (2) the presence of overlying organs anteriorly and posteriorly, (3) poorly explained variabilities in radiopharmaceutical concentration in the organ (in spite of various dietary regimens), and (4) high radiation dose to the patient due to the long physical half-life of  $^{75}\text{Se}$  (120 days) and the long biologic half-time of the agent (70 days). The general consensus appears to be that  $^{75}\text{Se}$ -L-selenomethionine scanning of the pancreas does not significantly contribute to the early diagnosis of cancer of the pancreas (8,9). Other extrastructurally labeled amino acids such as  $^{123}\text{I}$ -4-iodophenylalanine (10),  $^{123}\text{I}$ -5- and 6-iodo-tryptophan (10), and  $^{18}\text{F}$ -5- and 6-fluorotryptophan (11) have been synthesized but have not appeared to be promising pancreas-scanning agents.

The use of radiopharmaceutical agents labeled with positron-emitting short-lived radionuclides makes possible external detection by coincidence counting techniques such as positron emission computerized tomography, which has the advantages of improved resolution and localization independent of depth. This approach offers a new non-invasive in vivo probe for quantitative and metabolic studies in man. It is particularly appealing because metabolic precursors and physiologically active compounds can be labeled with  $^{11}\text{C}$  ( $T_{1/2} = 20$  min) or  $^{13}\text{N}$  ( $T_{1/2} = 10$  min) without changing their biological properties; therefore, accurate external physiologic and metabolic observations that are otherwise only possible by autoradiography ( $^{14}\text{C}$ ,  $^3\text{H}$ ) or other invasive analyses of excised tissue can be made. Furthermore, the use of short-lived radionuclides permits sequential examinations over short time intervals without undue radiation exposure to the patient.

The work proposed in this application involves the use of  $^{11}\text{C}$ -labeled amino acids in the diagnosis of pancreatic diseases by positron emission computerized tomography. Although most naturally occurring amino acids show a significant affinity for the pancreas, two of them, tryptophan and valine, appear from animal studies to have the highest degree of pancreatic specificity (5, 12-14).

Washburn, Hayes, and co-workers of this laboratory have developed methods for synthesizing  $^{11}\text{C}$ -labeled amino acids (15,16), and ours is at present the only laboratory in the United States that has used these agents in positron tomographic clinical investigations. The production method, a rapid, high-temperature, high-pressure modification of the Bücherer-Strecker amino acid synthesis, gives racemic mixtures of  $^{11}\text{C}$ -labeled amino acids. (Reference 16, attached as Appendix A, gives details of the method.)

Up to this point our clinical experience with  $^{11}\text{C}$ -labeled tryptophan and valine has been restricted to the DL racemates (17,18) because resolution methods rapid enough to be compatible with the 20.4 min  $T_{1/2}$  of  $^{11}\text{C}$  have not been developed for

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Research Plan: Significance (continued)

these amino acids. Likewise, no method that allows rapid  $^{11}\text{C}$ -labeling of the L-forms of valine and tryptophan has been devised.

In order to accomplish the main task of this proposal, namely to make a significant contribution to the differential diagnosis of pancreatic diseases, it is of utmost importance to use the L-isomer of either  $^{11}\text{C}$ -labeled tryptophan or valine for positron tomography of the pancreas. The optical isomers of amino acids show distinctly different behaviors in cancer and normal pancreatic tissue. Tamemasa (19) has shown that the L-isomers have a high affinity for normal pancreas, whereas the D-forms tend to localize preferentially in neoplastic lesions. Therefore, the DL-form would be expected to share the characteristics of both enantiomers and concentrate in normal pancreas and in pancreatic tumors to an approximately equal degree. We have observed such behavior with  $^{11}\text{C}$ -DL-tryptophan in our preliminary clinical studies. Thus by using the L-optical form of tryptophan or valine, we should be able to distinguish between functioning normal pancreas and any disease processes that are present. Malignant lesions could then be differentiated from benign, cystic, and inflammatory processes by using either  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC, alicyclic unnatural amino acids that show preferential uptakes in tumor tissue but no affinities for inflammatory lesions (20). This non-invasive technique could thus provide for the complete differential diagnosis of pancreatic diseases, hopefully at an early stage.

Recent studies by Comar and co-workers (21) with  $^{11}\text{C}$ -L-methionine and positron tomography show that neoplastic lesions of the pancreas do appear as defects in the normal pancreatic image. (The production method for  $^{11}\text{C}$ -L-methionine, methylation of L-homocysteine with  $^{11}\text{CH}_3\text{I}$ , is not applicable to other  $^{11}\text{C}$ -labeled amino acids.) These findings, coupled with our own observations and published reports, have prompted our interest in using  $^{11}\text{C}$ -labeled L-tryptophan or L-valine as differential pancreas-scanning agents in conjunction with  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC.

In collaboration with Dr. G. Digenis of the University of Kentucky, we have successfully resolved  $^{11}\text{C}$ -DL-phenylalanine into its D- and L-isomers by oxidative deamination using immobilized L- and D-amino acid oxidase, respectively (22). The yields for  $^{11}\text{C}$ -D- and L-phenylalanine were 19 mCi and 27 mCi. Purification was accomplished by cation exchange chromatography, and the optical purity was established by optical rotatory dispersion. Resolution and purification required 35 minutes. This enzymatic method should be applicable to the resolution of other  $^{11}\text{C}$ -labeled amino acids, including  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine.

Several reports (23-25) have appeared recently concerning direct resolution of amino acid enantiomers by high pressure liquid chromatography (HPLC). Although resolution of  $^{11}\text{C}$ -labeled amino acids has not yet been reported, the technique seems ideal for this application. The most promising HPLC method involves use of a stationary phase made by coupling optically active proline to a commercial HPLC packing and then complexing with cupric ions. The potential advantages of the HPLC method are its speed of separation and the fewer manipulations that are required, relative to the enzymatic method. The technique does not appear to be general for all amino acids, but fortunately tryptophan and valine are among the amino acids most suited to the method (23).

Another method uses a classical HPLC packing and a chiral mobile phase. However, this method is difficult to use in a preparative way because of the

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Research Plan: Significance (continued)

problems encountered in separating the mixture obtained by solvent evaporation of the isolated fractions; therefore, according to Audebert (26), it is recommended only for analytical purposes.

Stewart and Doherty (27) have completely resolved DL-tryptophan by affinity chromatography on bovine-serum albumin-agarose columns. This resolution is based on a highly specific biological property, the antipodal specificity in the binding of tryptophan to bovine-serum albumin. This appears to be the method of choice for resolving  $^{11}\text{C}$ -DL-tryptophan. The disadvantage of this method is its lack of generality for other amino acids.

The development of a method for rapidly resolving the L-form of amino acids from their DL-racemates as proposed in this project would be a significant contribution to basic research into the function of the human pancreas and to research in amino acid metabolism in general. It would open the door to in vivo assessment of uptake, kinetics and metabolism of natural, metabolizable amino acids in organs such as brain, heart, and liver, as well as the pancreas.

The success of the project depends on progress in the resolution of  $^{11}\text{C}$ -amino acid racemates but equally important is the development of computer capability and the acquisition of an updated ECAT scanner (equivalent to ECAT II). Correct staging of malignant tumors and objective evaluation and measurement of the response of tumors to therapy is not always possible. It is especially difficult to measure regression of tumors early after initiation of therapy, and a method that allows objective external measurement of biological/metabolic changes induced by treatment would be highly desirable. In this proposed research we will attempt to develop a biologic "caliper" to measure pancreatic tumor response to therapy by using quantitative positron emission computerized tomography to measure the fraction of  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC extracted by a tumor. This kind of test would be an extremely useful research tool for monitoring therapy, and it could be the basis for a simple test using an external counting method less sophisticated and less expensive than positron tomography.

### C. Preliminary Studies

On the basis of the partial success of diagnostic procedures with radiopharmaceuticals such as  $^{75}\text{Se}$ -L-selenomethionine, we have undertaken to try a series of related diagnostic methods that take advantage of several potential improvements:

(a) As stated above, certain amino acids show a greater tendency to concentrate in the pancreas than does  $^{75}\text{Se}$ -L-selenomethionine. In animal work carried out by ourselves (13,14) and others (5,12), both DL-valine and DL-tryptophan have been shown to have a high affinity for the pancreas. We have shown that these  $^{11}\text{C}$ -labeled amino acids can be rapidly synthesized and purified in quantities adequate for pancreas visualization in animals and man (15,16). Table 1 shows our production experience for the four  $^{11}\text{C}$ -labeled amino acids discussed in this proposal. (The method is quite general and is useful for production of many other  $^{11}\text{C}$ -labeled amino acids.) We are able to produce multiple batches of  $^{11}\text{C}$ -labeled amino acids at intervals of 1 hr or less by overlapping the various steps, i.e., generation of  $^{11}\text{C}$  activity, amino acid synthesis, amino acid purification, and column regeneration. In a typical all-day run, we routinely produce four or more batches of various  $^{11}\text{C}$  labeled amino acids for clinical or preclinical investigation.

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Research Plan: Preliminary Studies (continued)

Table 1  
<sup>11</sup>C-Labeled Amino Acid Production at M&HSD/ORAU  
 (Through January 31, 1980)

Amino Acid	Total Number Batches	Number Patients Studied	Total Activity (mCi)	Average mCi/batch	Highest Yield (mCi)
<sup>11</sup> C-DL-Valine	38	18	6,090	160	360
<sup>11</sup> C-DL-Tryptophan	57	51	6,730*	118	330
<sup>11</sup> C-ACPC	73	56	7,000*	96	300
<sup>11</sup> C-ACBC	40	33	5,420	135	420

\* In early development of these compounds the total yield was almost zero, so batch total and average per batch were quite low.

(b) We can take advantage of the special radiation characteristics of <sup>11</sup>C. Decay by positron emission is accompanied by the production of two annihilation photons emitted at an angle of 180° to each other. Using recently developed instrumentation that utilizes these coincident annihilation photons and the techniques associated with transmission computerized tomography, it is possible to reconstruct cross-sectional images that show three dimensionally the source of positron-emitting activity in the body (28,29). The distinct advantage of this type of imaging is that it provides high resolution and avoids image distortion due to overlying radioactivity and that the image is subject to quantitative analysis (30). The Medical and Health Sciences Division of Oak Ridge Associated Universities has applied a commercially available positron emission computerized tomographic scanner (ECAT I) to clinical investigations since May 1977. By combining the advantages of <sup>11</sup>C-labeled DL-tryptophan or DL-valine with this optimal type of imaging, it was anticipated that greatly improved pancreatic diagnostic results could be obtained. Carcinomas were expected to be seen as zones of decreased or absent concentration as is the case with <sup>75</sup>Se-L-selenomethionine.

(c) Based on this concept, we also developed a method for labeling the unnatural alicyclic amino acids l-aminocyclopentanecarboxylic acid (ACPC) and l-aminocyclobutanecarboxylic acid (ACBC) with <sup>11</sup>C because of their potential as tumor-localizing agents, particularly when used in conjunction with positron tomography (31,32). Thus <sup>11</sup>C-ACPC and <sup>11</sup>C-ACBC were developed for confirmatory studies on malignancies suspected on <sup>11</sup>C-DL-tryptophan or <sup>11</sup>C-DL-valine pancreas scans.

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Research Plan: Preliminary Studies (continued)

Our results have shown that positron tomographic imaging of the pancreas with  $^{11}\text{C}$ -carboxyl-labeled DL-tryptophan and DL-valine allows physiologic studies by imaging and has the potential to measure in vivo the utilization of metabolic substrates or analogs. Positron tomographic studies (examples are shown in Appendix B) supplement the morphologic information obtained by ultrasound (US) and transmission computerized tomography (CT). A group of 29 patients with proven or suspected pancreatic disease were examined with positron ECT; 18 of these subjects were also studied with US and transmission CT. In 26 patients with known clinical outcomes, positron tomography gave one false positive and three false negative results (17). Ultrasound and/or transmission CT failed to show three proven lesions. Increased uptake of  $^{11}\text{C}$ -DL-tryptophan delineated three pancreatic carcinomas and one lymphoma. In normal subjects positron tomography with these agents invariably showed the pancreas with striking clarity. These observations indicate that positron tomography provides a unique method for visualizing biologic activity and that quantitative analysis of amino acid utilization should be possible with this non-invasive technique. The fact that selective pancreatic localization of these agents occurs almost immediately after intravenous injection means that the short half-life of  $^{11}\text{C}$  rather than being a disadvantage is on the contrary actually an asset in terms of lowered radiation dose and the possibility of frequent repetition of scans.

We have shown the general usefulness of the unnatural amino acid  $^{11}\text{C}$ -ACBC as a tumor-localizing agent in conjunction with positron tomography. Our present experience with  $^{11}\text{C}$ -ACBC is limited to 33 patients. The variety of neoplasms that concentrate  $^{11}\text{C}$ -ACBC very rapidly after intravenous injections includes bronchogenic carcinoma, metastatic mammary Ca, lymphomas (33), and poorly differentiated carcinomas, as well as cancer of the pancreas.  $^{11}\text{C}$ -ACBC cannot be metabolized and shows promise as a useful tool for measuring the metabolic activity and/or the proliferative stage of tumor tissues.

Our finding that the racemic forms of  $^{11}\text{C}$ -valine and  $^{11}\text{C}$ -tryptophan localized to a significant degree in pancreatic neoplasms was unexpected. We had expected to see carcinomas as zones of decreased or absent concentration as is the case with  $^{75}\text{Se}$ -L-selenomethionine. Especially in view of findings published by Tamemasa et al (19), it is likely that the presence of the D isomer is responsible for the tumor affinity observed with the amino acid racemates we used in our studies.

A crucial factor involved in the success of the proposed project involves quantitation using an ECAT positron emission computerized tomograph. In the course of over two years experience in patient studies and intentional computer program challenges in phantom studies, we have observed some serious deficiencies in the performance of our ECAT; i.e., phantom studies indicate that reconstructed data, in terms of calculated image "quantity" versus "dose", is not a linear function. The amount of isotope measured in a particular region of a reconstructed image is both a function of the image size (34) and the amount of isotope present (a non-linear function, due to randoms)! The "measured" amount of activity in an area, as a function of time, if the effect of count rate were to be ignored, is of little significance in the pancreas, as the size of that organ does not change significantly. However, the ability of the pancreas to extract the various labeled agents which we propose to use, and therefore the relative amount of Compton and random scatter contributing to a calculation of relative isotope uptake, will influence our measurement of the rate of suppression (or lack thereof), of the cancerous tissues' growth. Our experience with calculations on phantoms has dramatically

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Research Plan: Preliminary Studies (continued)

shown the effect of both image size (equivalent in part to tumor size) and count rate (equivalent to tumor uptake) on quantification of our results. A 30% or greater variation in count rate per  $\text{cm}^2$  has not been uncommon in our data, despite efforts to correct the data for known non-linearities.

We have improved on the basic software provided with the original ECAT I system, initiating procedures involving multi-level transmission image data correction, Compton scatter correction, outlier data squelching, background subtraction routines, etc., but we are still in need of better data, as collected, to quantify and confidently analyze our results.

A new version of the ECAT, ECAT II, overcomes to a great extent the problems we have encountered with our ECAT I. We, therefore, propose to update our ECAT I electronically to an ECAT II and have accordingly included funds in our proposal to accomplish this during the first year of the project.

D. MethodsResolution of  $^{11}\text{C}$ -labeled amino acids

An essential part of this proposal is the development of synthetic techniques for rapidly resolving the racemic mixtures of  $^{11}\text{C}$ -labeled amino acids which result from the modified Bücherer-Strecker synthesis. Our production method (16) has produced up to 330 mCi of  $^{11}\text{C}$ -DL-tryptophan and 360 mCi of  $^{11}\text{C}$ -DL-valine in a total synthesis and purification time of 40-45 min, one-half of which is devoted to synthesis and the other half to chromatographic purification. (See Appendix A for details.) Because of our high production capability, we should, therefore, be able to separate the L-isomers from these racemates and still have more than an adequate amount of  $^{11}\text{C}$ -labeled L-tryptophan or L-valine for clinical studies ( $\sim 10$ -15 mCi will be required).

We propose to combine resolution and purification through use of recently developed chromatographic or enzymatic techniques. This should result in an overall synthesis, resolution, and purification time which is compatible with the 20.4 min half-life of  $^{11}\text{C}$ . This production time could, in fact, be no longer than the 40-45 min currently required for  $^{11}\text{C}$ -labeled racemic amino acids.

Based on our preliminary clinical studies using  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine (see Preliminary Studies) and animal studies by both our group (13,14) and others (5,12), tryptophan appears to be considerably more specific for the pancreas than valine. Proposed studies during the first year of support will further compare the two agents (see following section on proposed clinical investigations). If  $^{11}\text{C}$ -DL-tryptophan is indeed shown to be superior, our resolution efforts will be concentrated on this agent.  $^{11}\text{C}$ -DL-Valine will only be resolved if attempts to resolve  $^{11}\text{C}$ -DL-tryptophan should be unsuccessful.

The method of choice for resolution of  $^{11}\text{C}$ -DL-tryptophan appears to be affinity chromatography on bovine-serum albumin-agarose columns as reported by Stewart and Doherty (27). The stationary phase is prepared by linking defatted bovine-serum albumin to cyanogen bromide-activated Sepharose 4B by an ethylenediamine-succinic acid leash. The method is highly specific for resolving DL-tryptophan, utilizing the differential binding constants of bovine-serum albumin for the optical antipodes

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Research Plan: Methods (continued)

of this amino acid. The column is equilibrated with pH 9.2 0.1 M borate buffer, the racemic tryptophan mixture is loaded, and D-tryptophan is eluted with the same 0.1 M borate buffer. L-Tryptophan is then eluted with 0.1 M acetic acid. Excellent resolution was obtained with 500 nmol of DL-tryptophan on a 0.9 x 25-cm column with a flow rate of 30 ml/hr. For resolution of  $^{11}\text{C}$ -DL-tryptophan at the reaction scale now used (0.1 mmole), a larger column will be required, probably on the order of 2.5 x 25 cm. Column flow rates will be increased by using 7-9 psi of positive air pressure, as we currently do for our other column separations (16). It should be possible to use the bovine-serum albumin-agarose affinity column as a preliminary purification step (in place of the Porapak Q column which we now use), followed by cation-exchange chromatography for final purification and concentration of the  $^{11}\text{C}$ -L-tryptophan solution.

If the resolution of  $^{11}\text{C}$ -DL-tryptophan described above should unexpectedly fail, high pressure liquid chromatographic (HPLC) methods will be employed for resolution of this amino acid or  $^{11}\text{C}$ -DL-valine. Many reports have appeared in the literature in recent years concerning the use of chiral stationary phases for the direct resolution of racemates by ligand-exchange chromatography (23-25). For resolution of amino acid racemates, an optically active amino acid, usually L-proline, is coupled to a stationary phase suitable for HPLC and the resulting resin is complexed with metal ions, normally cupric ions. The modified stationary phase is then packed into an HPLC column by conventional techniques. The mobile phase is typically water or an aqueous buffer system. With L-proline, the D-amino acid is usually eluted first, but it should be possible to reverse this order and thus save time by using D-proline instead of L-proline in the preparation of the stationary phase. The work to date with these methods has been limited to analytical applications; however, by using larger, semi-preparative HPLC columns, it should be possible to resolve  $^{11}\text{C}$ -labeled amino acid racemates at the 0.1 mmole reaction scale which we generally use. The HPLC method may be used by itself or it may be necessary to use the method for resolution and preliminary purification, followed by final purification and concentration using cation-exchange chromatography, as discussed above for affinity chromatography.

We have communicated (Appendix C) with Drs. B. Lefebvre and R. Audebert of Laboratoire de Physico-Chimie Macromoléculaire, l'Université Pierre et Marie Curie, Paris, France, about the availability of a chiral hydrophilic gel which they used with great success in the resolution of several racemic amino acid mixtures (24). These researchers kindly replied (Appendix D) that the hydrophilic packing is to be manufactured by an industrial firm in the near future and promised to send us a sample when it becomes available.

Should the chromatographic methods described above not be successful for resolving  $^{11}\text{C}$ -DL-tryptophan or  $^{11}\text{C}$ -DL-valine, we will use the enzymatic method developed by Dr. G. Digenis of the University of Kentucky School of Pharmacy in collaboration with our research group (22). Dr. Digenis has agreed to act as a consultant to this project at no charge (see Biographical Sketch). The method has to date been used only for resolution of  $^{11}\text{C}$ -DL-phenylalanine but should be quite easily adaptable to other  $^{11}\text{C}$ -labeled amino acid racemates, including  $^{11}\text{C}$ -DL-tryptophan and  $^{11}\text{C}$ -DL-valine. The procedure involves oxidative deamination using the appropriate immobilized amino acid oxidase (AAO); i.e., if the L-enantiomer is desired, as in the proposed clinical studies, the immobilized D-AAO would be used to cause selective degradation of the unwanted D-enantiomer. For the  $^{11}\text{C}$ -DL-

1079434

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Research Plan: Methods (continued)

phenylalanine resolution studies, L-AAO was immobilized on diazotized arylamine glass beads and D-AAO was bound to cyanogen bromide - activated Sepharose 4B. Immobilized L-AAO and D-AAO were incubated at 37° with buffered <sup>11</sup>C-DL-phenylalanine solutions at pH's of 6.8 and 9.0, respectively. The optically active amino acid in each case was separated from phenylpyruvic acid (the product of oxidative deamination) by cation-exchange chromatography. In the <sup>11</sup>C-DL-phenylalanine studies, the resolution and purification were done on a previously purified racemic amino acid solution. Therefore, 35 min was required in addition to the 40-45 min needed for production of the purified <sup>11</sup>C-amino acid racemate, for a total of 75-80 min. We will evaluate the feasibility of eliminating the preliminary separation steps and using the crude reaction mixture directly for enzymatic resolution. This would result in a saving of ~ 20 minutes, giving a net production time of 55-60 min, which is compatible with the short half-life of <sup>11</sup>C.

The proposed schedule for resolution of <sup>11</sup>C-labeled amino acids is as follows: (1) During the first year the various resolution methods will be evaluated largely using unlabeled compounds. A limited number of developmental cyclotron runs would also be required during the latter part of the first grant year. (2) In the second year of grant support, technique development will be completed, requiring an increased number of developmental cyclotron runs. Tissue distribution studies using the <sup>11</sup>C-labeled resolved amino acid to be studied clinically will be performed in two animal species in support of an Investigational New Drug (IND) application to be filed with the U.S. Food and Drug Administration; the agent will then be made available for clinical use during the latter part of the second grant year. (3) During the third grant year the <sup>11</sup>C-labeled resolved amino acids will be made available for continued clinical trials.

Clinical Investigations

Clinical investigations using <sup>11</sup>C-labeled amino acids in conjunction with positron emission computerized tomography will be divided into three phases over the 3-year study period.

During the first year emphasis will be placed on comparison of <sup>11</sup>C-ACPC and <sup>11</sup>C-ACBC and of <sup>11</sup>C-DL-tryptophan and <sup>11</sup>C-DL-valine with regard to differential uptake in pancreas versus tumor in patients with strongly suspected pancreatic carcinoma. By the end of the first year the updated ECAT scanner (ECAT II) will be available for clinical use and our studies will be expanded beyond imaging into quantitative measurements of amino acid concentrations in pancreatic tumors before, during, and after treatment (see Quantitative Imaging). Late in the second year the <sup>11</sup>C-labeled L-form of tryptophan or valine is expected to be available for clinical use. These clinical studies will then be completed in the third year.

Clinical investigations in the first year will first focus on comparing <sup>11</sup>C-ACPC and <sup>11</sup>C-ACBC using positron tomography in patients with suspected pancreatic carcinoma to determine whether <sup>11</sup>C-ACPC might have an advantage over <sup>11</sup>C-ACBC in the diagnosis of pancreatic tumors. Our previous experience with <sup>11</sup>C-ACPC and rectilinear scanning (20) has shown that little <sup>11</sup>C-ACPC is taken up by the human pancreas, but high concentrations of this unnatural amino acid have been observed in pancreatic tumors. On the other hand <sup>11</sup>C-ACBC seems to concentrate almost as well in normal pancreas as in tumors of the pancreas. <sup>11</sup>C-DL-Tryptophan and <sup>11</sup>C-DL-valine will be similarly compared to further investigate the apparently greater

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Research Plan: Methods (continued)

pancreatic specificity of  $^{11}\text{C}$ -DL-tryptophan found in preliminary studies. In a separate study, we are planning to investigate the efficacy of  $^{11}\text{C}$ -labeled amino acids in conjunction with positron tomography for assessing the response of pancreatic carcinoma to therapy. This group of patients will be examined before, during and after therapy with  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC and  $^{11}\text{C}$ -DL-tryptophan or  $^{11}\text{C}$ -DL-valine (depending on the results of the initial comparison of the two pairs of amino acids). Positron tomography will be performed with a reference source of activity placed in the field of view to facilitate absolute quantitation when the ECAT II system becomes available (delivery and acceptance testing to require approximately 4-5 months from date of order). The protocol for the first year is outlined in the following table (Table 2):

Table 2

Clinical Investigations During First Year

<u>No. Patients</u>	<u>Patient Selection Criteria</u>	<u>Scanning Agent</u>
10	Strongly suspected pancreatic Ca (pain, weight loss, steatorrhea and jaundice)	$^{11}\text{C}$ -ACPC and $^{11}\text{C}$ -ACBC on same day
5	As above	$^{11}\text{C}$ -DL-tryptophan and $^{11}\text{C}$ -DL-valine on same day
5	Patients receiving chemotherapy and/or radiation therapy for pancreatic Ca*	$^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) and $^{11}\text{C}$ -DL-tryptophan (or $^{11}\text{C}$ -DL-valine) on same day x 3

\* Positron tomography scans with the two preferred scanning agents will be done before, during and after a course of therapy.

Table 3 lists the clinical information needed for the patients selected for the studies outlined in Table 2.

Table 3

Clinical Information Required

<u>General</u>	<u>Laboratory Tests</u>	<u>Radiographic Studies (not mandatory)</u>	<u>Experimental Studies</u>	<u>Acceptable Confirmatory Examinations</u>
History and Treatment	Serum amylase Urine amylase CEA Lipase	GI series Barium enema Gallbladder	Transmission CT Ultrasound ECAT positron tomography Endoscopy	ERCP with cytology Directed biopsy Surgery Subcutaneous cholangiogram Arteriogram

1079436

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Research Plan: Methods (continued)

The endpoints of the first year's studies will be the following:

1. Decision on the superiority of  $^{11}\text{C}$ -ACPC or  $^{11}\text{C}$ -ACBC for selectively imaging pancreatic cancer with positron tomography.
2. Decision on the superiority of  $^{11}\text{C}$ -DL-tryptophan or  $^{11}\text{C}$ -DL-valine for imaging normal pancreatic tissue with positron tomography.
3. Complete scan data collection on five patients receiving treatment for pancreas carcinoma for quantitative analysis during second year of funding period with ECAT II capability.
4. Determine correct diagnosis.
5. Determine morbidity and risk factors.

During the second year we anticipate that we will have available an accurate quantitative ECAT II system for in vivo metabolic studies in patients with pancreatic cancer and chronic relapsing pancreatitis. Use of the updated ECAT system (ECAT II) should not only yield data amenable to quantification, but should also give us the advantage of simultaneous image reconstruction conjoint with image acquisition; this will allow for immediate rescanning, thus providing efficiency in instrument use. In the second year we will expand the series of quantitative in vivo studies by 10 patients in the pancreas cancer therapy group and also study 10 patients with chronic pancreatitis during different phases of their disease. Each patient will be examined three times during the course of the disease as outlined in Table 4.

In addition, we project that  $^{11}\text{C}$ -L-tryptophan (or  $^{11}\text{C}$ -L-valine) will become available for clinical use during the latter part of the second grant year. Therefore, five patients with suspected pancreatic carcinoma will be studied using  $^{11}\text{C}$ -L-tryptophan (or  $^{11}\text{C}$ -L-valine) in conjunction with  $^{11}\text{C}$ -ACPC (or  $^{11}\text{C}$ -ACBC) in a preliminary test of this regimen for differential diagnosis of pancreatic carcinoma.

Table 4

Clinical Investigations During Second Year

<u>No. Patients</u>	<u>Patient Selection Criteria</u>	<u>Scanning Agents</u>
10	Patients receiving chemotherapy and/or radiation therapy for pancreatic Ca*	$^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) and $^{11}\text{C}$ -DL-tryptophan (or $^{11}\text{C}$ -DL-valine) x 3
10	Patients with chronic pancreatitis*	$^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) and $^{11}\text{C}$ -DL-tryptophan (or $^{11}\text{C}$ -DL-valine) x 3
5	Patients with suspected pancreatic Ca	$^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) and $^{11}\text{C}$ -L-tryptophan (or $^{11}\text{C}$ -L-valine)

\* Positron tomography scans will be done with the two preferred scanning agents at several stages of the disease.

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Research Plan: Methods (continued)

The clinical information needed is the same as that indicated in Table 3. Endpoints of the studies projected for the second year are to:

1. Determine the effect of successful treatment and tumor progression on the uptake of  $^{11}\text{C}$ -ACPC (or  $^{11}\text{C}$ -ACBC) and  $^{11}\text{C}$ -DL-tryptophan (or  $^{11}\text{C}$ -DL-valine) in patients undergoing therapy for pancreatic carcinoma.
2. Determine the effect of the phase of pancreatitis on the uptake of the same agents.
3. Determine whether ECAT II techniques can be applied to quantitate accurately amino acid extraction/utilization by tumors of the pancreas.
4. Determine whether the prognostic information obtained with this approach corresponds with the clinical response to therapy.

During the third year clinical studies with  $^{11}\text{C}$ -L-tryptophan (or  $^{11}\text{C}$ -L-valine) in conjunction with  $^{11}\text{C}$ -ACPC (or  $^{11}\text{C}$ -ACBC) to determine the potential of this method for the non-invasive, accurate diagnosis of pancreatic carcinoma will be completed. In addition the quantitative studies in patients undergoing treatment for pancreatic carcinoma will continue through the third year. The outline for the clinical studies during the third year is given in Table 5.

Table 5

Clinical Investigations During Third Year

<u>No. Patients</u>	<u>Patient Selection Criteria</u>	<u>Scanning Agents</u>
10	Suspected pancreatic carcinoma	$^{11}\text{C}$ -L-tryptophan (or $^{11}\text{C}$ -L-valine) and $^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC)
15	Patients with proven pancreatic carcinoma undergoing chemotherapy*	$^{11}\text{C}$ -L-tryptophan (or $^{11}\text{C}$ -L-valine) and $^{11}\text{C}$ -ACPC (or $^{11}\text{C}$ -ACBC) x 3

\* Patients in this group will be scanned one time each before, during and after the first course of cyclic chemotherapy.

Endpoints of clinical investigations in the third year will be to:

1. Verify in humans the potential utility of positron tomography using a combination of a natural  $^{11}\text{C}$ -labeled L-amino acid to visualize the normal pancreas and an unnatural  $^{11}\text{C}$ -labeled amino acid for the differential diagnosis of pancreatic disease.
2. To provide evidence that in vivo measurements of amino acid extraction/utilization by pancreatic cancer could be applied to accurately gauge the response of such cancers to therapy.
3. To collect information for a comparative cost analysis between conventional staging and gauging procedures used in developmental chemotherapy protocols and the in vivo measurements of the proliferative activity of pancreatic cancers as planned for this proposal.

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Research Plan: Methods (continued)Quantitative Imaging

It is well recognized that unwanted scattered radiation events occur as a function of scattering medium and count rate. True coincidence counting and the development of high quality images and accurate quantitation is the goal of positron tomography systems with their associated computational programs.

In our present system (ECAT I), singles, accidental coincidences, and scattered coincidence events tend to mask the true coincidence data. Extraneous events, accepted as true events, have accounted for up to 60% of the data collected in scans of phantoms using this system.

In several of our phantom studies we have made attempts to linearize the response of our system to known concentration levels in the field of view. Computation techniques used have included background subtraction of data from the collected images and the development of software to estimate body densities and produce a refined body attenuation estimate for use in back projection algorithms.

Consistently, we have found that whatever technique we use, our correction scheme must take into account the total count rate of the system. For example with a low count rate phantom we found it best to back project using an 8% background subtract figure, but the same phantom required almost a 16% correction when the phantom count rate was four times as high.

The addition of a delayed coincidence gate and other associated hardware and software improvements available in the ECAT II system would allow us to estimate the amount of "random" coincidences occurring in the image as it is collected and permit real time or later "randoms" correction. While this technique will not remove all unwanted events, it will tend to linearize the system with respect to its present intensity versus count rate nonlinearities. At this point, our image correction routines could be more appropriately, and presumably universally, applied.

We shall specifically therefore continue software development which will yield improved images, by acquiring experience with both patient and phantom studies, and applying and upgrading our analysis schemes. Our present schemes, as mentioned, include operations such as background subtract, outlier squelching, normalization, transmission data file manipulation, etc. It is anticipated that some combination of these methods, including perhaps an as yet untried Compton scattering correction routine, will yield a computational protocol which will be invariant from phantom to phantom, count rate independent, and linear.

Listed below are some of the computation techniques we will study:

## 1. Emission Data Corrections:

## a. Background subtraction techniques

- (1) Constant value
- (2) Percentage of maximum
- (3) Ramp(s) calculated from data files to edge of body
- (4) Combinations of 1,2,3
- (5) Nonlinear amount based upon square of count rate

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Research Plan: Methods (continued)

- b. Blanking outside body outline
- 2. Transmission Data Corrections
  - a. Single level transmission data estimation
  - b. Multilevel body outline estimation
  - c. Data bounding, smoothing
- 3. Transmission-corrected Emission Data
  - a. Data bounding (outlier squelching)
  - b. Data projection normalization
  - c. Randoms subtraction (linear and nonlinear)

Our approach to quantification will include detailed studies on the effects of scattered radiation on the quality of our collected data. For example, a typical human torso, if modeled as an ellipse, might be 15 cm along the short axis and 30 cm along the long axis. A point source, located at the origin of this ellipse, would not be equally sensed in all projections, due to varying thicknesses of material between the source and sensor. In fact, using an attenuation coefficient of  $0.1 \text{ cm}^{-1}$ , only 7.4 to 22.5% of the radiation would be sensed in any given projection, compared to the non-attenuated case.

At 511 keV, for water, only 35% of incident gamma rays are absorbed in Compton scattering, the remainder are primarily forward scattered albeit at a degraded energy level. It is apparent from our phantom studies that some of this forward scattered radiation must be being detected, as calculations on both emission and transmission data show increases in count rate levels over that predicted by theory for phantoms with attenuation. This data has been confirmed both by comparing sensed radiation levels for various phantoms involving several levels of activity, and by comparing transmission data through known thicknesses of water with that of air. Further, from observation of all phantom and patient data, we note that radiation is sensed in all areas of the initial data files where there is only air present.

Preliminary data has indicated to us that the Compton scattering phenomena, at least as measured in air outside our phantoms, might be mathematically modeled as arising from a convolution of an exponential function with an apparent true distribution. The rate of fall of the exponential function seems somehow to be related to the attenuation properties of the phantom. An explanation for this behavior will be one of our goals.

E. Facilities Available1. Laboratory space

Our equipped radiopharmaceutical development research space consists of 2 large (750 sq. ft. each) and 2 smaller laboratories (500 sq. ft. each), all with fume hoods. A positive pressure "clean room" with 2 vertical laminar flow benches (1 recirculating, 1 exhaust) is available for final preparation of labeled materials before administration to patients.

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Research Plan: Facilities Available (continued)2. Cyclotron Complex

The Oak Ridge National Laboratory's 86-inch cyclotron accelerates protons to an energy of 22 MeV; internal beam intensities up to 3000  $\mu$ A are available. It has 8-inch wide dees and 4-inch dee-to-dee and dee-to-ground spacing and operates at 9,000 oersteds at a frequency of 13.4 Mc/sec. Three 20-inch oil diffusion pumps provide high pumping speed, moving 15,000 liters/sec at the operating pressure of  $3 \times 10^{-6}$  torr. An alteration to the 86-inch cyclotron which will permit rapid, remote changing of targets is to be installed in the spring of 1981; this should result in greater cyclotron availability. A hot cell is located approximately 50 ft. from the cyclotron. This hot cell has power-assisted manipulators and a hoist on an overhead rail which can be maneuvered over most of the cell area.

3. Animal Facilities

Adequate space is available for housing of animals on the 3rd floor of the existing Medical and Health Sciences Division building on Vance Road. The facility is accredited by the American Association for Accreditation of Laboratory Animal Care, and care of the animals is under the supervision of a veterinarian, Dr. Conrad B. Richter. Established standards of laboratory animal care, promulgated by the DHEW [Publication No. (NIH) 72-73] will be observed.

4. Clinical Studies

Clinical tests will be carried out at the Oak Ridge Associated Universities Medical and Health Sciences Division facilities in Oak Ridge. The patients will come from referring physicians at the Oak Ridge Hospital, the Knoxville hospitals, and other nearby institutions such as Vanderbilt University. The Medical and Health Sciences Division has a long history of cooperation with referring physicians and demonstrated ability to attract patients for experimental work. All proposed clinical studies will receive prior approval from the ORAU Human Studies Committee and the U.S. Food and Drug Administration before they are carried out in patients. Informed consent will be obtained for each study.

5. Equipment

## a. Nuclear medical instrumentation

1. ORTEC ECAT-I whole body positron emission computerized tomograph which will be upgraded to an ECAT II version.
2. Pho/Gamma V scintillation camera.
3. Ohio Nuclear dual-head rectilinear scanner modified for coincidence detection.
4. Associated equipment for monitoring and administering radio-pharmaceuticals.

## b. Other equipment

1. Two HPLC chromatographs.
2. HPLC refractive index and variable wavelength UV detectors.
3. HPLC gradient generator and strip chart recorder with computing integrator.
4. Four peristaltic pumps and fraction collectors with UV monitors and recorders.

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Research Plan: Facilities Available (continued)

5. Data Trac.
6. Packard liquid scintillation counter.
7. Packard refrigerated automatic gamma-scintillation counter.
8. Cary Model 14 recording spectrophotometer.

6. Oak Ridge Scientific Community

The surrounding scientific institutions employ many individuals who are now and can in the future be helpful in a variety of ways. Of these the Nuclear Medicine Technology Group at the Oak Ridge National Laboratory is the closest at hand and the University of Tennessee with its various disciplines and departments as well as the Memorial Research Center is nearby in Knoxville. A variety of basic and clinical disciplines are represented at the Medical and Health Sciences Division itself, i.e., pathology, cytogenetics, radiobiology, ultrastructural anatomy, biochemistry, and immunology.

Use of Department of Energy (DOE) Facilities and DOE Contract Requirements

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

It is believed that in large measure the requirements of the DOE contract parallel conditions which NIH ordinarily applies to its grants. In the event of differences between NIH grant terms and the DOE 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 DOE for direct resolution with NIH.

By way of general information, ORAU's contract with the DOE is a cost-type contract financed under a Government-fund account. The specific contract work is formulated in cooperation with the DOE and authorized within general guidelines in the contract. Contract terms include DOE responsibilities for Government ownership and control of inventions, data, and other research products. Ownership of all equipment and facilities acquired by ORAU with DOE 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.

F. Collaborative Arrangements

The radiopharmaceutical development/nuclear medicine programs of the Oak Ridge Associated Universities Medical and Health Sciences Division have a long-standing collaborative arrangement with Oak Ridge National Laboratory, particularly the Nuclear Medicine Technology group (Health and Safety Research Division) and the staff associated with the 86-inch Cyclotron (Operations Division). These collaborative ties will be very important in the proposed project.

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Research Plan: Collaborative Arrangements (continued)

Mr. A.P. Callahan of the Nuclear Medicine Technology group will be a consultant to the project and will be involved in hot cell operation and general consultation in the area of radioactive syntheses. The 86-inch Cyclotron and associated hot cell facilities are to be made available for production of the  $^{11}\text{C}$ -labeled amino acids which will be used in the proposed studies.

Dr. Paul King of the Department of Biomedical Engineering, Vanderbilt University, Nashville, Tennessee, will also be a consultant to the project. Dr. King has a high level of expertise in the area of software development for improved computer applications with the ECAT positron tomographic scanner.

Dr. George Digenis of the School of Pharmacy, University of Kentucky, Lexington, Kentucky, has collaborated with us on the enzymatic resolution of  $^{11}\text{C}$ -labeled amino acid racemates. He will be a consultant in the proposed resolution studies.

Drs. I. R. Collmann of University of Tennessee Memorial Research Center and Hospital, Knoxville, Tennessee, and G. Avant, Vanderbilt University Hospital, Nashville, Tennessee, are gastroenterologists who will refer patients for the proposed studies and consult with the principal investigator on the clinical protocols to be followed and the interpretation of the clinical data.

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.

\_\_\_\_\_  
Date

\_\_\_\_\_  
Karl F. Hubner, M.D.  
Principal Investigator"

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H. APPENDIX

- A. Reprint of reference 16 (Washburn, L.C., Sun, T.T., Byrd, B.L., et al. High-level production of C-11-carboxyl-labeled amino acids. In Radiopharmaceuticals II, Proceedings of 2nd International Symposium on Radiopharmaceuticals, Seattle, Wash., 1979, pp. 767-777).
- B. Examples of positron tomographic scans obtained with  $^{11}\text{C}$ -labeled amino acids.
- C. Letter from Dr. Lee C. Washburn to Dr. Bernard Lefebvre inquiring about the availability of a chiral hydrophilic gel for resolution of amino acid racemates by high pressure liquid chromatography.
- D. Reply to above letter (Appendix C).

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