PROGRESS REPORT

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BIOMEDICAL RESEARCH WITH CYCLOTRON PRODUCED RADIONUCLIDES

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1. BIOMEDICAL RESEARCH WITH CYCLOTRON PRODUCED RADIONUCLIDES

OBJECTIVE:

The operation of the cyclotron has the following objectives:

(a) Research on nuclear reactions and target design for production of radionuclides.

(b) Research on labeling of biologically important compounds with cyclotron produced radionuclides.

(c) Production of radionuclides and labeled compounds for metabolic isotope research in patients and in animals carried out by the metabolic isotope study section.

(d) Development of improved cyclotron operation and beam handling technology.

SUMMARY OF CYCLOTRON USE:

Table 1 is a summary of runs performed with the cyclotron during this report period. A run indicates a separate request for cyclotron time, usually of several hours duration, and may include many short runs for a few minutes. Beam-on-time is the time the anode or Dee voltage was on, and represents 40% of the available working hours (3024). The oscillator filament meter registered 1625 hours or 52% of the available working hours.

TABLE 1

Summary of Cyclotron Operations

January 1, 1979 to June 30, 1979

Radionuclide	No. of Runs*	Beam on Time (hrs)	Use
^{18}F	144	234.4	Clinical bone scans
	38	84.4	Haloperidol, estradiol labeling
	32	27.5	Anhydrous HF development
	7	6.1	Precursor, phantom studies
^{11}C	51	200.8	^{11}CO clinical studies
	6	23.0	^{11}C -AIB development
	14	40.5	^{11}C precursor development
	4	12.4	Valine labeling
^{13}N	72	204.4	Glutamate clinical studies
	34	84.5	Amino acid, ammonia labeling
	23	81.4	Nitrosamine labeling
	2	4.6	PET scans
^{15}O	11	48.9	Steady state studies
^{53}Fe	26	43.5	Clinical bone scans
^{38}K	18	22.0	Animal, human studies
$^{27}\text{Al}, ^{75}, ^{76}, ^{77}\text{Br}$	9	9.9	Production, cross-section studies
^{19}Ne	4	4.0	Feasibility studies
^{62}Zn	2	1.7	Feasibility studies
	11	29.2	Neutron dosimetry
	29	45.0	Cyclotron testing, operator training
	537	1208.2	

Other Use**	Hours
Cyclotron research & development	41.0
Cyclotron maintenance	144.8
Cyclotron repair	152.8
Operator training	27.6
	366.2

* Represents a scheduled time slot. 2-6 batches are normally made in a run.

** Not included in radionuclide section above.

2. EVALUATION OF CHEMOTHERAPEUTIC REGIMENS IN OSTEOGENIC SARCOMA,
ADENOCARCINOMA AND OTHER SOLID TUMORS WITH N-13-L-GLUTAMATE AND
N-13-L-GLUTAMINE (Supported in part by NCI #CA-18153).

OBJECTIVE:

This project is directed toward the detection of tumors and their metastases before treatment and toward an assessment of the influence of chemotherapy on tumor metabolism of labeled amino acids.

SCOPE OF INVESTIGATION:

During this report year, it was proposed to broaden the spectrum of tumors studied, starting with untreated patients and observing the effect of therapy on tumor uptake of N-13 from labeled sodium L-glutamate. In selected osteosarcoma cases it was proposed to compare the effect of therapy on the diphosphonate scan with its effect on N-13 uptake after the administration of glutamate. It was also desired to add to the series of Ewing's sarcomas studied and to extend the series to other sarcomas.

RESULTS AND CONCLUSIONS:

Lymphangiosarcomas in two patients were studied and found to take up moderately increased amounts of N-13 after injection of labeled sodium-L-glutamate. Both of these patients had follow-up studies during their course of chemotherapy and displayed reduced tumor uptake, although tumors were still visualized in each case. Metastatic disease in lung, present in one of the patients was not identifiable in the glutamate scan.

A 41 year old man with a malignant fibrous histiocytoma of the right thigh showed very high uptake of N-13. The uptake diminished but was still high after one month of therapy.

A sarcoma developing in the humerus of a patient with Paget's disease of the bone was studied with N-13 glutamate, Tc-99m methylene diphosphonate and Ga-67 citrate. The sarcoma collected more of each of these labels than did Pagetoid bone, which also showed increased uptake of all agents relative to normal bone. The behavior of MDP and Ga-67 citrate remained the same after one month of high dose methotrexate therapy.

A germ cell tumor growing in the lung and mediastinum of a young man took up N-13 derived from labeled sodium L-glutamate. Some, but not all, of the lesions of chondrosarcoma in two patients were detected with N-13 glutamate. A fibrosarcoma in one patient was positive and its uptake increased during chemotherapy. Negative results were obtained in a recurrent leiomyosarcoma, a rhabdomyosarcoma of the pelvis and a patient with adenocarcinoma of unknown origin.

Six patients with Ewing's sarcoma were studied. The primary lesion was well seen in all, but metastases were not visualized in two. There was a good response of tumor uptake to chemotherapy in three patients undergoing four serial studies. These subjects are still being followed to be sure the clinical course is as favorable as the scans indicate.

Eleven patients with brain tumors have been studied with N-13 L-glutamate. This group ranged in age from 4 to 21 years and consisted of 6 females and 5 males. All had evidence of recurrent disease as documented by transmission computed tomography (TCT). Table 2 summarizes the findings for this group. In general, the lesions were equally well seen with N-13 L-glutamate as with TC-99m pertechnetate. However, one notable exception was a primitive neuroectodermal tumor (Figure 1), which showed a tumor-to-normal tissue ratio of 7.1, compared to 2.3 for pertechnetate. Tumor-to-normal tissue ratios for other subjects where quantitative pertechnetate data were available are shown in Table 3.

We have performed 58 additional N-13 glutamate studies in 33 patients with osteogenic sarcoma since January 1979. Most of these studies were performed to evaluate the effects of preoperative adjuvant chemotherapy on the primary tumor. In the course of studying these patients, we have also obtained further information on the factors that affect N-13 uptake by this tumor following administration of labeled glutamate.

(1) Correlation with Tumor Blood Supply:

It was previously shown that there is a relationship between the uptake of ^{13}N by the primary tumor and the degree of neovascularity as determined by arteriography (see Table 4). This study was extended in a patient with a primary osteogenic sarcoma of the proximal tibia using the three-dimensional distribution of N-13 glutamate obtained with the PC-4200 positron tomograph; to determine the regional blood supply the distribution of C-11 carbon monoxide labeled red cells was also assessed. Figure 2 shows the distributions of these agents in a transaxial section of the lesion. The soft tissue extension on the anterior aspect of the left proximal tibia shows a central area of decreased N-13 uptake; this area presents as a region of decreased vascularity in the C-11 CO image. Apparently only those tumor cells in the relatively well-vascularized periphery of the tumor are actively taking up N-13.

(2) Correlation with the Degree of Tumor Viability:

It was previously shown that the degree of ablation of N-13 uptake during preoperative adjuvant chemotherapy was positively correlated with the degree of necrosis of osteogenic sarcoma as determined by histologic examination of surgically resected specimens (see Table 5). We performed a detailed analysis of the relationship between the fractional decrease in N-13 uptake and histologic response by generating computer-produced "quotient images", which yielded pixel-by-pixel values of the changes in N-13 uptake in the presurgery scan relative to the pretreatment baseline scan. When the tumor was surgically resected, the specimen was cut longitudinally into thin (0.5 cm) slices with a circular bone saw and a representative slice chosen. That slice was further cut into squares about

Figure 1. Left-lateral view of head of a seven year-old female patient with primitive neuroectodermal tumor in both frontal lobes, showing the distribution of N-13 in the tumor and salivary glands after the i.v. administration of N-13 labeled L-glutamate.

TABLE 2N-13 Glutamate and Tc-99m in Primary Brain Tumors

<u>Subject</u>	<u>Diagnosis</u>	<u>N-13</u>	<u>Tc-99m</u>
		<u>Glutamate</u>	<u>Pertechnetate</u>
PL	Embryonic Pineal gland ca	positive	positive
MiSca	CNS dysgerminoma	positive	-
MeScu	pineoblastoma	positive	positive
JB	anaplastic glioma	positive	positive
EV	PNET	positive	positive
AM #1	medulloblastoma (pre- therapy)	positive	positive
AM #2	medulloblastoma (post- therapy)	positive	positive
JC	PNET	positive	positive
MP	astrocytoma	negative	negative
LO	medulloblastoma	negative	positive
IL	medulloblastoma	negative	positive
LE	meningeal sarcoma	positive	positive

TABLE 3

Tumor/Normal Ratios for N-13 and Tc-99m

<u>Subject</u>	<u>Diagnosis</u> ¹	<u>N-13 Ratio</u> ²	<u>Tc-99m Ratio</u> ²
P.L.	Embryonic pineal ca.	2.2	2.8
Me. Scu.	Pineoblastoma	2.8	2.7
J.B.	Anaplastic glioma	1.2	(not measured)
E.V.	PNET	7.1	2.3
A.M.	Medulloblastoma	2.4	1.8
Mi. Sca.	Dysgerminoma	(not visualized)	(not measured)
J.C.	PNET	3.2	2.9

¹ Diagnosis from histologic specimens. In some cases, tumors were recurrent after previous therapy.

² Tumor to normal brain ratios were calculated from digital right- or left-lateral images. The maximum count-rate in the tumor was divided by the count-rate in adjacent normal brain to obtain the ratio.

Submitted images were produced from digital data with correction for the physical decay of N-13 and displayed in a dot-density format using an electrostatic printer-plotter. Each displayed level represents 5% of the range of counts from 0 to maximum. Quantitative imaging system has constant-response collimators and a resolution of 2.0 cm (FWHM) at 511 keV.

TABLE 4N-13 Glutamate Uptake vs Arteriographic Findings

<u>Subject</u>	<u>Lesion Site</u>	<u>Grade (% dose)</u>	<u>Arteriogram Findings</u>
CW	Dist. Femur	4	Hypervascular lesion
PM	Dist. Femur	4	Hypervascular lesion
JB	Dist. Femur	4	Faint opacification of mass w/demonstration of tumor vessels in soft tissue component.
SF	Prox. Tibia	4	Diffusely incr. abnormal vascularity
MF	P. Humerus	2	Abnormally increased vascularity
SM 2	P. Humerus	2	Mild neovascularity; some tumor strain
TM 2	P. Humerus	2	11x13 cm mass w/incr. vascularity
TM 1	P. Humerus	2	Small areas of abnorm. incre. vasc.
SP 3	Dist. Femur	2	Very minimal vascularity in tumor
FF	Dist. Femur	2	Abnormally increased vas. w/moderate tumor staining
JK 2	Dist. Femur	1	Normal Arteriogram - no tumor vasc.
LB 2	Prox. Femur	0	No abnorm. vascularity; no soft tissue mass delineated
DM	Pelvis	0	Avascular lesion
MV	Pelvis	0	Avascular lesion

Figure 2. Transaxial section through both proximal tibiae in an eleven year-old girl with osteogenic sarcoma in the left tibia, performed using the PC-4200. a) Image obtained with N-13 L-glutamate. Tumor (arrow) is seen on anterior aspect of the left tibia and shows a central area of decreased uptake. b) image obtained after inhalation of C-11 carbon monoxide (yielding labeled red cells). Vessels emerging from the left popliteal space are seen, as well as a "ring" of increased activity corresponding to the region of increased N-13 uptake.

TABLE 5. Correlation Between N-13 Glutamate Uptake and Histology

<u>Subject</u>	<u>Pretherapy uptake</u>		<u>Changes in Gutamate Scan*</u>	<u>Histology Change**</u>
	<u>UI</u>	<u>grade</u>		
JR		4	93 percent decrease (pre-op scan normal)	4-
VD		4	83 percent decrease	3
RA		4	67 percent decrease (pre-op scan normal)	3
JK		4	55 percent decrease	3
PM		4	42 percent decrease	1
WS		3	40 percent decrease	3
CH		1	40 percent decrease (post-chemo scan nearly normal)	3
SP		2	37 percent decrease	3
LA		4	20 percent decrease	1
RS		4	20 percent decrease	1
PB		3	18 percent decrease	2
SM		2+	17 percent decrease	2
PMC		1	8 percent decrease	2
CT		3+	7 percent decrease	2

- continued -

TABLE 5 -- continued

<u>Subject</u>	<u>Pretherapy uptake</u>		<u>Changes in Glutamate Scan*</u>	<u>Histology Change**</u>
	<u>UI</u>	<u>grade</u>		
KD		1	7 percent increase	2
TM		2	15 percent increase	1
LL		4	30 percent increase	2
CW		4	74 percent increase	1

* Glutamate change - Increase or decrease (relative to pre-therapy base-line study) of approximate percent dose in the primary tumor as measured by the HEG system.

** Histology change grades - Effect of pre-operative chemotherapy based on multiple sections of resected primary tumor:

1. Little or no effect identified
2. Areas of acellular tumor osteoid, necrotic and/or fibrotic material attributable to the effect of chemotherapy, with other areas of histologically viable tumor.
3. Predominant areas of acellular tumor with osteoid, necrotic and/or fibrotic material attributable to the effects of chemotherapy with only scattered foci of histologically viable tumor cells identified.
4. No histologic evidence of viable tumor identified within the specimen.

2 cm x 2 cm squares, which were thin-sectioned and stained with hematoxylin and eosin. The position of the sections in the specimen was carefully noted, and correlated with 4 pixels in the quotient image. The degree of tumor necrosis in each small section was estimated by microscopic examination, and the results correlated with the percent change in glutamate uptake at that point in the quotient image. The results for 71 sections from 6 patients are shown in Figure 3. It appears that reductions in glutamate uptake of more than 40% are highly associated with total tumor necrosis. Increases in glutamate uptake are frequently associated with high degrees of residual tumor cell viability. Hence it is probable that N-13 glutamate uptake partially reflects the number of viable cells in the primary tumor.

There continues to be good correlation between the decreased glutamate uptake and the clinical response of the patients to high-dose methotrexate therapy. Progression of disease paralleled increased glutamate uptake in 3 patients. The changes in the Tc-99m methylene diphosphonate (MDP) bone scan paralleled the changes in the N-13 glutamate scan during chemotherapy. Table 6 shows the quantitative changes in N-13 glutamate and Tc-99m MDP uptake in primary osteogenic sarcoma for two patients in whom simultaneous N-13 and Tc-99m images were acquired with the HEG system. Table 7 correlates the qualitative changes in N-13 and Tc-99m uptake for those patients where quantitative MDP images were not available. In some cases the change in the glutamate scan is more marked than the change in the MDP scan.

To more accurately determine the venous blood clearance of N-13 L-glutamate, fifteen small (0.5 ml) samples were withdrawn from an antecubital vein in one patient during the interval from 0-3 minutes post-injection in the contralateral arm. The clearance curve is depicted in Figure 4. As observed previously in normal volunteers (based on fewer samples), the clearance is very rapid, with most of the activity being diluted in the vascular system and extracted by skeletal muscle, heart, liver and pancreas in the first 80 seconds after injection. The activity appears to clear the blood with a half-time of 45 seconds.

In one patient, a sample was drawn at seven minutes post-injection, at which time approximately five percent of the activity remained in the blood. The plasma was removed, deproteinized in ice-cold picric acid and subjected to high-pressure liquid chromatography (HPLC) in an effort to determine the chemical form of the N-13 in the blood. The counting rate in the HPLC effluent was too low to permit an accurate quantitative analysis of the distribution of the label. Qualitatively, the activity appears to be predominantly in the form of neutral amino acids (e.g., glutamine, alanine, etc.) or urea, along with a smaller amount of glutamate.

RELATIONSHIP BETWEEN REGIONAL N-13 GLUTAMATE UPTAKE
CHANGE AND RESIDUAL TUMOR CELL VIABILITY

FIGURE 3

% CELLS NECROTIC

% CELLS VIABLE

TABLE 6

Quantitative Changes in N-13 Glutamate and Tc-99m MDP Tumor Uptake
During Chemotherapy for Osteogenic Sarcoma

<u>Subject</u>	<u>% Change from Baseline</u>	
	<u>N-13</u>	<u>Tc-99m</u>
JV	+125%	+40%
SS	-31%	-15%

TABLE 7

Correlation of Changes in Glutamate and Bone Scans During
Chemotherapy

		<u>Tc-99m</u>		<u>MDP</u>		
		↑↑	↑	NC	↓	↓↓
N-13 <u>GLU</u>	↑↑	-	-	1	-	-
	↑	-	-	-	-	-
	NC	-	-	1	2	1
	↓	-	-	3	2	1
	↓↓	-	-	3	3	4

NC = no change

single arrow = increase/decrease

double arrow = marked increase/decrease

3. PANCREATIC IMAGING WITH ^{13}N -L-AMINO ACIDS

OBJECTIVE:

This project is directed toward the evaluation of ^{13}N -L-glutamate and other amino acids labeled with 10-minute nitrogen-13 for pancreatic visualization by means of the PCT-4200 camera for making focal-plane and/or transaxial tomographic projections in organs.

SCOPE OF INVESTIGATION:

Initial studies were focused upon our observations of N-13 in pancreatic images following intravenous injection of enzymatically-synthesized ^{13}N -glutamate, in the natural L-form, into normal volunteers and into patients suspected of harboring pancreatic cancers or having pancreatitis.

These studies constitute the initial applications here of the PCT-4200 (Cyclotron Corporation, Berkeley, CA) "positron camera" for imaging distributions of nitrogen-13 in 2-dimensional, tomographic, longitudinal, coronal, focal-plane projections and in 3-dimensional, tomographic, transaxial, 1.0-cm-thick (FWHM) "slices" of the human pancreas and other organs, made at 1.4-cm sequential spacing.

RESULTS AND CONCLUSIONS:

Pronounced accumulations of nitrogen-13 were seen in the pancreas, heart, and liver of a 70-year-old white male imaged 45 minutes after intravenous injection of ^{13}N -glutamate (Figure 5).

Three transaxial tomographic slices of his pancreas made 5-35 minutes after injection of ^{13}N -L-glutamate are shown in Figure 6, and five slices made through his heart appear in Figure 7.

Rapid and marked accumulation of nitrogen-13 in the pancreas and liver of this volunteer also were observed in 2-dimensional projections made both with the PCT-4200 and with the HEG scanner when ^{13}N -L-valine was injected into him intravenously. But, by contrast with the findings after ^{13}N -L-glutamate, little nitrogen-13 appeared in his heart after ^{13}N -L-valine.

Similar findings occurred in a second human volunteer after i.v. ^{13}N -L-glutamate; but positive images have not been observed thus far in patients having cancer of the pancreas. These studies are continuing; and it is planned to extend them to study the effects of pancreatitis, of various foodstuffs, and times of ingestion on the images.

The rapid and marked accumulation of the nitrogen-13 in the pancreas, heart and liver after intravenous ^{13}N -L-glutamate suggests explorations of the effects of cancer chemotherapeutic drugs, such as adriamycin, on the phenomena, especially in respect to the uptake of the nitrogen-13 by the heart and/or the liver.

Figure 5: Heart, Liver and Pancreas of 70 years old man visualized with ^{13}N -glutamate

Figure 6: Tomographic section of Pancreas shown in Figure 6, made on PC 4200 using ^{13}N -glutamate

Figure 7: Tomographic section of heart shown in Figure 6, made on PC 4200 using ^{13}N -glutamate

4. TOMOGRAPHIC SKELETAL IMAGING WITH ^{18}F -FLUORIDE

OBJECTIVE:

This study is directed toward the evaluation of ^{18}F sodium fluoride for use in skeletal imaging in the transaxial tomographic projection.

SCOPE OF INVESTIGATION:

Conventional bone scans display three dimensional distribution of increased mineral turnover as two dimensional images, making interpretation difficult. It was intended in the initial studies to determine if transaxial tomography using $\text{Na } ^{18}\text{F}$ would increase diagnostic accuracy of bone imaging in some patients.

RESULTS AND CONCLUSIONS:

Sixty-two studies have been carried out in the past year, including 21 studies in patients with thoracic tumors, 20 patients with suspected neoplastic involvement near the knee joint, 15 with pelvic cancers, and 5 with skull and cranial tumors. About half of the patients had osteogenic sarcoma and the remainder had various tumors with associated skeletal metastases.

The general impression from these first studies is that tomographic visualization of the thorax and skull provides information qualitatively superior to that obtained from the conventional bone scans. Transaxial tomography of primary tumors in the extremities also help to determine the precise extent of involvement in the soft tissue or intramedullary cavity. Examination of the pelvis helps to differentiate activities in the bladder, ileal conduit or bony structure. In most pelvic examinations, however, the ^{18}F tomography only confirms what has been shown in the conventional bone scan.

5. BICARBONATE POOL VISUALIZATION USING $^{11}\text{C}\text{O}_2$

OBJECTIVE:

The objective of this study is to delineate tumors in humans by external imaging using the $511\text{ keV} \pm \gamma$ -rays emitted incidentally to the decay of carbon-11 with the use of the PCT-4200 PET camera.

SCOPE OF INVESTIGATION:

Studies were initiated this year to evaluate ^{11}C -carbon dioxide as a skeletal and tumor imaging agent, to compare its effectiveness with existing agents and to discern what special advantages might be gained in terms of selectivity, resolution, and dose reduction. The construction of the hot atom transfer system (HATS) which has allowed continuous delivery of short lived radioactive gases into the clinical areas, the special appeal of non-invasive administration of radiolabeled agents by inhalation, and the availability of the PC-4200 for positron emission tomography provided the impetus for a reinvestigation of this agent. Twelve $^{11}\text{C}\text{O}_2$ studies were performed in the report interval, one in a normal volunteer and the remainder in patients with osteogenic sarcoma.

RESULTS AND CONCLUSIONS:

Increased uptake of ^{11}C in the tumor region was noted in all ten patients. The amount of C-11 in soft tissues was appreciable, however, and delineation of the bone tumor was not as distinct as that seen in the bone tumor scans carried out with fluorine-18. Uptake of C-11 in the upper abdomen of the volunteer was also noted, but it was uncertain whether this might have indicated the presence of ^{11}C -bicarbonate in the pancreatic juice.

Dynamic studies were performed in most patients, prompt uptake of C-11 was noted in the bone tumor as well as in corresponding areas of normal bony structure. The C-11 appeared to remain in situ with little loss during the entire 15 minute interval. Due to poor statistics, the reconstituted transaxial images were rather poor, and it was difficult to differentiate the alterations inside and surrounding the tumor mass.

Since C-11 appeared to reach the tumor and bony structures promptly, and to remain there with little loss during the 15 minutes of observation, data should be collected immediately following the inhalation of $^{11}\text{C}\text{O}_2$ in order to increase formation density and to improve the quality of the images being reconstituted by the computer.

Studies to correlate the findings of the $^{11}\text{C}\text{O}_2$ distribution with those of bone tumor metabolism by means of other bone-seeking radionuclides are planned.

6. VASCULAR CHANGES IN LUNG EXPOSED TO RADIATION (Supported by NHLBI 5 R01 HL22371)

OBJECTIVE:

The major objective of this study is to develop non-invasive and safe methods useful for in vivo monitoring of the effects of radiation and chemical treatment on normal and diseased tissues within humans. Carbon-11 labeled carbon monoxide is used to measure changes in circulating hemoglobin volume in primary carcinoma within lung and in normal lung resulting from radiation treatment. Comparison of early changes with the presence or absence of radiation pneumonitis and late changes with tumor recurrence may yield data important for improving treatment. This ¹¹CO method is being extended to the quantitative measurement of circulating hemoglobin blood volumes in a variety of tumors in humans in an attempt to measure a first order criteria of tumor response to chemical therapy; namely, the accessibility of the chemical to the tumor provided by an adequate vascular system.

SCOPE OF INVESTIGATION:

To add about 20 patients and to continue follow-up of previously entered patients where appropriate. To further develop our methods for analysis, especially for the tomographic data.

RESULTS AND CONCLUSIONS:

Twenty-five new patients have taken part in a total of 41 studies involving the use of the Positron Camera Tomograph (PCT4200) during the period from 6/1/79 to 6/1/80. Five studies were carried out using the HEG scanner. Overall, we have completed 87 studies involving 37 patients since the beginning of this grant (9/1/78). The PCT4200 has allowed us to observe in 2-dimension (focal plane tomography) and in 3-dimension (transaxial computed tomography) tumors located within a variety of body regions including heads, shoulders, arms, hands, abdomen, legs and feet. The tumors have included bronchogenic carcinoma, osteogenic sarcoma, Ewing's sarcoma, pseudo neuroectodermal tumors, malignant schwannoma, teratoma, liposarcoma, hemangiosarcoma, and neuroblastoma.

Thirteen of the 25 new patients have had repeat studies carried out after significant chemical and/or radiation treatment. Three patients with lung tumors have follow-ups in excess of one year, only one remains alive. The other patients have as many as five follow-up studies extending to eighteen weeks.

In the lung cancer patients, serial scans were obtained during the course of radiation therapy in addition to a pre-therapy baseline study. The baseline and post-therapy scans were aligned and computer-processing was used to calculate, point-by-point the percent change in C-11 uptake. This regional map of the change in C-11 content relative to baseline reflects the local changes in vascularity. In general, the irradiated lung region shows a marked increase in blood volume (hyperemia) during

the treatment procedure, which then decreases with time as fibrosis takes effect. A late increase in the vascular content of the irradiated portion of the lung is considered consistent with tumor recurrence. An increase in the vascular volume was also seen in the contralateral lung region during therapy.

An illustrative case is that of D.F., who in Nov. 1978 received 4500 rad in 3 weeks to his mediastinum and right main stem bronchus for a proved epidermoid carcinoma of the lung. By Jan. 1979, his chest was asymptomatic, but by May 1979 he had developed shortness of breath, which we attribute to radiation fibrosis.

In Dec. 1979, progress of disease was evident by x-ray with some cavitation. Patient expired Apr. 20, 1980 (1-1/3 years after diagnosis).

Our ^{11}CO studies paralleled the clinical course. In the first week of treatment hyperemia (quantitated at greater than 135%) of irradiated lung was demonstrated. In the next two weeks, the hyperemia decreased by about 10%. Following the radiation treatment decreased vasculature was observed until clinical evidence of tumor regrowth appeared, at which time revascularization could be seen.

The unirradiated ipsilateral lung showed variable vascular changes, which we interpret as compensatory and/or the result of atelectasis and pneumonitis. The most dramatic compensatory changes appeared in the opposite (unirradiated) lung with a maximum at 19 days after completion of RT and a second maximum appearing shortly before the patient's death.

Our studies including earlier animal work (1) indicate that vascular volume changes can be clearly documented in irradiated tissues using ^{11}CO . The correlations with clinical regression or regrowth of tumor which we have observed show promise for clinical application.

This study represents a first step toward the development of non-invasive and low hazard methods for performing quantitative measurements of the circulating hemoglobin volume throughout the body. The analysis of vascular circulating hemoglobin volume changes produced by radiation therapy in cases of inoperable lung cancer represents an area where 2-dimensional quantitative imaging may prove adequate for assessing the effectiveness of radiation therapy on tumor destruction as well as on normal tissue tolerance in the radiation treated lung volume. As this study and other studies which require 3-dimensional tomography progress in a variety of body tissues, we anticipate this method will provide a non-invasive alternative to angiography which will be more powerful in its quantitative aspects, in that it will provide a direct measurement of capillary volume in addition to major vessel integrity. It will not, however, provide the high resolution visualization of the major and intermediate size components of the vascular system that angiography does. It can be anticipated that this method will improve the diagnosis and therapy evaluation of disease and/or therapy which produces vascular damage within the body.

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7. ASSESSMENT OF POTASSIUM-38 AS A MYOCARDIAL AGENT

OBJECTIVE:

To obtain preliminary evidence regarding the applicability of Potassium-38 as an agent for assessing the myocardium.

SCOPE OF INVESTIGATION:

Initial studies were focused upon the observations of ^{38}K localization and persistence in laboratory animals and in normal human volunteers. These studies constitute the initial applications of the PCT-4200 (The Cyclotron Corporation, Berkeley, California) positron camera for imaging with ^{38}K .

RESULTS AND CONCLUSIONS:

Initial studies revealed that ^{38}K accumulates almost maximally in the hearts of dogs and monkeys within a few minutes. Clearance of labeled potassium was estimated to have a half time of about 6 hours.

Two human subjects have been studied with K-38, using the dynamic, focal plane and tomographic modes of the PCT-4200.

WGM is a 72 year old white male, weighing 80 kg. He received 12 mCi of Potassium-38 (iv). The resulting dynamic image revealed maximum accumulation in the heart at 2 minutes; a clearance half time was estimated to be 2.6 ± 0.7 hours. Two dimensional focal plane images of the heart were obtained, but the residual activity was not sufficient for tomographic imaging. A comparative study using K-38 was performed using the SKI HEG scanner operated in the coincidence mode. The myocardium was readily visualized and dynamic studies showed the clearance half time of K-38 from the heart region to be 3.01 ± 0.49 hours.

E.K. is a 30 year old white female weighing 59 kg. She received 7.3 mCi of K-38 (iv). The resulting dynamic image showed maximal myocardial uptake within a few minutes and a clearance half-time in the heart region of 3.9 ± 1.0 hours. The focal plane mode showed high accumulations of Potassium-38 in the heart, liver, kidneys and spleen, but again tomographic sections of the heart were not obtained because of low activity.

It is planned to continue these studies and to expand them to include cancer patients with myocardial disfunctions resulting from therapeutic intervention in treatment of their disease, to determine any significant changes which might be observed in terms of total K-38 uptake, time of maximal uptake, or persistence in the myocardium.

8. IRRADIATION OF OSSEOUS TUMORS WITH $^{32}\text{P}/^{33}\text{P}$ -HEDP (supported by the William Rankin and Elizabeth Forbes Rankin Grant of the American Cancer Society, PDT-141).

OBJECTIVE:

The goal of this study is the development and clinical implementation of 1-hydroxy-ethylidene-diphosphonate (HEDP) labeled with β^- emitting isotopes of phosphorus as an agent for therapy of metastatic osteogenic sarcoma and skeletal metastases of other tumors.

SCIENTIFIC SCOPE OF PROPOSED RESEARCH:

Studies conducted in the past year were developed to determine hematopoietic effects of ^{32}P -HEDP alone and in combination with high dose methotrexate with citrovorum factor rescue in patients with metastatic osteogenic sarcoma.

RESULTS AND CONCLUSIONS:

Three patients with biopsy proven metastatic osteogenic sarcoma were treated with test doses of ^{32}P -HEDP to make an evaluation of normal tissue tolerance to moderate levels of the radioagent and to demonstrate tumor localization and retention.

S.C. was a 21 year old white female who was first seen in July of 1977, with a complaint of right side pain. A skeletal survey showed abnormalities of the 5th rib and in the right knee. She was put on the BCD/HDMTX regimen and in September 1977. She underwent resection of the right chest wall and had a partial pneumonectomy. Chemotherapy was continued and in February 1978, she underwent an en'bloc resection of the right knee. In January 1979, she showed signs of paraplegia. A myelogram showed a block at T5/T6. She was treated by RT (3000 rads) in the T-3/T-8 vertebrae. A spinal fusion and laminectomy were performed. By October 1979, she had received 39 treatments of HDMTX. An increased uptake in the bone scan at T5/T6 suggested a change in treatment, and adriamycin and cis-platinum were started. Her condition worsened and in January 1980, this treatment was discontinued and the HDMTX regimen was resumed. She received her last HDMTX treatment in March 1980 and two days later was administered about 1.0 mCi of ^{32}P -HEDP. A scan of the resulting ^{32}P distribution was made after 1 hour showing high uptake in the T5/T6 region and in the right chest walls (Figure 8).

A large fraction of the injected dose was retained at those sites as only about 3% of the injected activity appeared in the urine. Serial bone marrow counting showed no ^{32}P activity at any time. The patient reported no relief from bone pain in the several days following administration of the radionuclide. Her serum alkaline phosphatase levels diminished by about 25% over the next few days. There was a precipitous drop in her platelet count which was characteristic of HDMTX treatment.

Within 2 weeks this had returned to her pretreatment level. White blood cell counts and hemoglobin counts were severely depressed for several days following HDMTX/HEDP- ^{32}P treatment. At the end of March 1980, the patient was admitted to Memorial Hospital. She showed a steadily declining platelet count and a greatly elevated WBC count and serum alkaline phosphatase. She was supported by palliative treatment and blood transfusions. The patient died at the end of April 1980, approximately 7 weeks following HEDP treatment.

E.H. was a 14 year old white male with a six month history of pain and swelling in the left proximal tibia. This was shown by biopsy to be an osteogenic sarcoma. Small lesions were also revealed in the right acetabulum, the iliac crests, the 12th right rib, the proximal right humerus, the right and left clavicle and the thoracic spine (T-3). In addition, a major lesion was noted in the lumbar spine. Following administration of 3.12 mCi (657 mg) of ^{32}P -HEDP, imaging was begun on the HEG scanner. The left and right tibias, a six inch wide strip of the lumbar spine and the pelvis were scanned.

The tumor in the left tibia was clearly observed (Figure 9). There was no apparent uptake in the contralateral region. The region in the lumbar spine was also seen clearly (Figure 10). However, the affected pelvic regions did not show ^{32}P localization. It was estimated that in the first hour, approximately 6.5% of the injected activity had localized in the lesion in the left tibia and 3.1% in the lumbar spine. Cumulative collection of urine showed that about 39% of the administered dose was excreted in the first 24 hours and about another 4.5% over the next six days.

There was no discernable effect of the HEDP on either the blood parameters or the level of serum alkaline phosphatase. The patient reported relief from bone pain for several days following administration of the dose. Eight days following ^{32}P -HEDP administration, the tumor in tibia contained a level of activity equivalent to 6.8% of the injected dose. Analysis of labeled species in the patient's urine showed that there were no metabolic products of HEDP.

Two months following the initial treatment, he was treated with 1.9 mCi (70.5 mg) of ^{32}P -HEDP. The 24 hour retention of HEDP increased in this period from 60% to 75% based on urinary excretion. Samples of the patients bone marrow did not reveal any detectable amounts of ^{32}P activity. Again there was no observable effect upon the platelet count, WBC or serum alkaline phosphatase levels. About a month following the second treatment, the patient suffered a severe and permanent depression of platelet and white blood cell counts, but in consideration of his course of disease and treatment no conclusions could be drawn. Six months following the initial treatment, extensive bleeding at the primary site was the basis for a decision to amputate the left leg above the knee. The patient succumbed to his disease shortly after.

Figure 8: ^{32}P -HEDP image of thoracic spine made on HEG scanner 1 hour post administration. Dark areas indicate regions of tumor at T-3 and in right rib area.

Figure 9: ^{32}P -HEDP image of lumbar spine made on HEG scanner 1 hour post administration. Dark area corresponds to region of tumor.

Figure 10: ^{32}P -HEDP image made on HEG scanner 1 hour post administration. Activity seen left tibia is in contrast to normal uptake in contralateral limb.

The third patient, S.E. was a 15 year old white male who had undergone a left hemipelvectomy osteogenic sarcoma. A residual tumor mass remained in the right pelvis. Following administration of 2.0 mCi (75 mg) ^{32}P -HEDP, no localization of ^{32}P activity was detected at this site. The patient died shortly after and no follow-up data was obtained.

These studies show that at dose levels of up to 0.044 mCi/kg there appears to be no acute or long lasting effects on the hematopoietic system which can be attributed to HEDP. Although both patients showed decreased platelet counts in the period following HEDP- ^{32}P administration, this was the result of a progressive decline which preceded radionuclide therapy. There are no observable positive effects upon osteogenic sarcoma at this dose level despite selective localization and low turnover rates in the tumor. Future studies will be directed toward further establishment of safety at this level and testing of progressively higher levels of ^{32}P -HEDP dose.

9. Ru-97 TRANSFERRIN AS A TUMOR-LOCALIZING AGENT

OBJECTIVE:

To survey Ru-103 and Ru-97 labeled transferrin as potential tumor-localizing radiopharmaceuticals and to compare their tissue distribution to Ga-67 citrate.

SCOPE OF INVESTIGATION:

This project was undertaken as a collaborative effort with Powell Richards and colleagues at Brookhaven National Laboratories (BNL). Ruthenium, an analog of iron, is labeled in vitro to human transferrin (an iron-carrying protein). All labeling was performed at BNL. Ru-97 is a nuclide with favorable physical characteristics for imaging ($T_{1/2} = 2.9$ d; primary gamma energy = 215 keV). However, Ru-103 transferrin was used in a majority of the tissue distribution studies because of the long physical half-life ($T_{1/2} = 39.8$ d).

The distribution of Ru-103 transferrin was studied in heterotransplanted human tumors in the nude mouse. Several mice were simultaneously injected with Ga-67 citrate for comparison. A volume of 0.1 cc of the radiopharmaceutical was injected into the retro-orbital venous plexus in anesthetized animals. Animals were sacrificed at 48 hours post injection; various tissues were removed, weighed and then counted in the gamma spectrometer (Packard). The relative concentration of the radiopharmaceutical in each tissue was determined.

Ru-97 transferrin was used to image a spontaneous tumor in a dog. The Ru-97 transferrin was also used to determine the blood clearance in the dog and in the mouse.

RESULTS AND CONCLUSIONS:

The results of the tissue distribution study are shown in Table 8. The relative concentration of Ru-103 transferrin is high in the liver, spleen, kidney, adrenals, skin, blood and some tumor types. Ga-67 citrate relative concentration is also high in liver, spleen and kidney in addition to being high in the intestine, bone and salivary glands. The dual isotope studies show that the tumor concentration of the Ru-103 transferrin is up to 1.9 times higher than the Ga-67 citrate, except for the primitive neuroectodermal tumor (PNET) in which the Ga-67 citrate concentration is 1.5 times higher than that of the Ru-103 transferrin. The Ru-103 transferrin concentration in blood is more than 5 times that of Ga-67 citrate, resulting in a lower tumor to blood ratio for the Ru-103 transferrin compared to Ga-67 citrate.

A favorable aspect of the Ru-103 transferrin is its low concentration in intestine compared to Ga-67 citrate. Ga-67 citrate has not been found to be the most optimal tumor-localizing agent for imaging abdominal tumors because of the high intestinal activity, even after laxatives and enemas have been used (1). Ru-103 transferrin may be of value in abdominal tumor

localization, especially if an interval longer than 48 hours were allowed between injection and imaging for the blood levels to decrease or some type of blood correction were applied.

Twenty-one mice were injected in the retro-orbital venous plexus with 15 μ Ci in 0.1 cc of Ru-97 transferrin. Three animals were sacrificed at each of the following times post injection: 30 minutes, 1, 4, 24, 46, 67 and 93 hours. Whole blood, liver, spleen and muscle were removed, weighed and counted. Heparinized capillary tubes of blood were also obtained at the same time intervals to determine the amount of activity in the plasma and red cell fraction. The data are plotted in Figs. 11 and 12. Most of the activity in the blood is in the plasma fraction which is not surprising since transferrin is normally found in plasma (2). Less than 4% of the relative concentration in plasma is in the red cell fraction. This small amount may be accounted for by plasma trapped in the red cell fraction (3). As seen in Fig. 10, the clearance of Ru-97 transferrin is slow from the liver and spleen. This finding is not surprising since the liver and spleen are known to be storage sites for iron (2).

One imaging study was performed using Ru-97 transferrin in a dog with a spontaneous tumor. A 10 year old German shephard dog was injected with 600 μ Ci of Ru-97 transferrin in 8 cc. The dog, weighing 55 pounds, has an ulcerated fibrosarcoma of the left ear involving the lymph glands of the neck with metastases to the lung, in addition to a mammary tumor. Images of the head were taken 79 hours later on an Ohio-Nuclear LFOV camera with simultaneous images being stored on a Gamma-11 system in a 64 x 64 matrix. The dog was then injected with 10 mCi Tc-99m human serum albumin (HSA) and imaged 5 minutes later with the dog still in the same position as for the Ru-97 transferrin image.

The Ru-97 transferrin image was normalized to the same number of counts over the heart region as in the Tc-99m HSA image (Fig. 13). A subtraction of the Tc-99m image (Fig. 14) from the normalized Ru-97 image (Fig. 13) resulted in the "subtraction image" shown in Fig. 15. The Ru-97 transferrin image shows increased uptake in the region of the tumor. The contribution of the increased uptake due to increased vascular pool is low as seen in the Tc-99m HSA image and resultant "subtraction image". The subtraction image also shows a high uptake in the region of the scapulas, probably in the marrow spaces.

Serial blood samples were taken at 1, 4, 24, 48 and 79 hours post-injection and were counted compared to a standard. The blood clearance of the dog is plotted in Fig. 11 and is compared to the clearance in mouse blood. The clearance of Ru-97 transferrin from the blood in the dog is slower than in mice.

Ruthenium labeled transferrin is believed to be a tumor-localizing agent analogous to Ga-67 citrate because of its association with transferrin. According to several investigators, Ga-67 citrate binds to transferrin in vivo (1). Ruthenium has been found not to label transferrin in vivo, hence in vitro labeling must be performed (4). Ga-67 transferrin binds to a specific transferrin receptor on the tumor cell. Binding is followed by intracellular incorporation with gallium deposition in lysosomes. The gallium is later distributed into storage sites with iron (as ferritin),

in addition to deposition in microvesicles and rough endoplasmic reticulum. Not all tumors are detected with Ga-67 citrate. Only about 66% of malignant tumors are detected with Ga-67 citrate and most that are detected are lymphomas (1).

Ru-97 and Ru-103 chloride have been reported to localize in various malignant tumors (5). Studies in patients reveal high uptake in liver, spleen and kidney with increased uptake in various tumors and inflammatory lesions. Clearance of activity from blood is slow therefore imaging was performed 3-6 days post injection. According to these investigators, ruthenium labeled to some other complex may be a better imaging agent providing its blood clearance was faster.

The results of this study so far seem to indicate that ruthenium-labeled transferrin has potential as a tumor-localizing agent. The low concentration of activity in the intestine may make it advantageous over Ga-67 citrate. A study in a dog with an ulcerated fibrosarcoma gave quite suitable images. Further studies should be performed to see what tumors concentrate this agent and whether or not it is specific to tumors. Correction for the higher blood levels seen with Ru-97 transferrin have been shown to be easily corrected by accumulating either simultaneously or shortly after, a blood image with Tc-99m HSA to provide a blood subtracted image.

TABLE 8

Relative Concentration 48 hrs Post Injection

	<u>Ru-103 Transferrin</u> mean $\pm$ S.D. (n)*	<u>Ga-67 Citrate</u> mean $\pm$ S.D. (n)*
Normal Skin	1.97 $\pm$ 0.98 (7)	0.83 $\pm$ 0.40 (4)
Tumor: Oat Cell	1.64 $\pm$ 0.83 (2)	0.91 $\pm$ 0.51 (2)
Malignant Schwannoma	1.10 $\pm$ 0.47 (2)	0.57 (1)
Primitive Neuroectodermal	1.59 $\pm$ 0.41 (2)	2.47
Malignant Melanoma	0.84 (1)	-
Synovial Sarcoma	0.75 (1)	-
Sarcoma	1.59 $\pm$ 0.16 (2)	-
Blood	1.46 $\pm$ 0.41 (10)	0.25 $\pm$ 0.13 (4)
Muscle	0.37 $\pm$ 0.15 (8)	0.16 $\pm$ 0.06 (4)
Liver	1.86 $\pm$ 0.38 (10)	1.80 $\pm$ 0.39 (4)
Spleen	1.62 $\pm$ 0.48 (10)	1.34 $\pm$ 0.36 (4)
Kidney	1.47 $\pm$ 0.38 (10)	1.78 $\pm$ 0.69 (4)
Heart	1.06 $\pm$ 0.21 (10)	0.29 $\pm$ 0.06 (4)
Lungs	1.14 $\pm$ 0.27 (9)	0.63 $\pm$ 0.08 (3)
Stomach (cleaned)	0.42 $\pm$ 0.13 (10)	1.39 $\pm$ 0.34 (4)
Intestine	0.57 $\pm$ 0.12 (9)	2.25 $\pm$ 0.94 (3)
Brain	0.08 $\pm$ 0.03 (10)	0.07 $\pm$ 0.03 (4)
Femur	0.58 $\pm$ 0.21 (9)	2.04 $\pm$ 0.44 (4)
Urine	1.24 $\pm$ 0.44 (7)	0.44 $\pm$ 0.16 (4)
Testes	0.83 $\pm$ 0.18 (6)	0.30 $\pm$ 0.10 (4)
Uterus	0.99 $\pm$ 0.11 (2)	-
Salivary Glands	1.01 $\pm$ 0.17 (10)	1.60 $\pm$ 0.59 (4)
Adrenal Glands	2.68 $\pm$ 0.88 (8)	1.22 $\pm$ 0.63 (4)

TABLE 8 - continued

Thyroid	0.78 ± 0.15 (6)	1.33 ± 0.17 (3)
Pancreas	0.45 ± 0.11 (2)	0.56 ± 0.32 (2)
% Total Body Retention	86.4 ± 9.8 (10)	59.4 ± 3.6 (4)

*n is the number of animals

Fig. 11

Clearance of Ru-97 transferrin from blood in a dog and in mice.

Fig. 12

Clearance of Ru-97 transferrin from liver, spleen and muscle in mice.

Fig. 13

Normalized Ru-97 transferrin image of dog showing increased uptake in tumor by left ear.

Fig. 14

Tc-99m HSA image of dog showing that the contribution of increased uptake of Ru-97 transferrin due to increased vascular pool is low.

Fig. 15

Tc-99m HSA image subtracted from normalized Ru-97 image of dog resulted in this "subtraction image".

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10. LABELED TERTIARY DIAMINES AS TUMOR-LOCALIZING AGENTS

OBJECTIVE:

To survey Se-75 labeled di- β -(morpholinoethyl)-selenide (MOSE) and di- β -(piperidinoethyl)-selenide (PIPSE) as possible tumor localizing agents.

SCOPE OF INVESTIGATION:

This study was undertaken in collaboration with M. Blau and H. Kung of the State University of New York at Buffalo. Kung and Blau have recently proposed a new class of radiopharmaceutical for the measurement of brain function (1). They developed PIPSE and MOSE, Se-75 labeled N-substituted diamines, which are neutral and lipid-soluble at blood pH (7.4). These molecules can diffuse into cells, but become charged and no longer lipid-soluble if the intracellular pH is lowered. These compounds have been shown to cross the blood brain barrier and become trapped in the intracerebral space where the pH is 7.0.

Tissues other than brain, such as heart and tumors, have also been shown to have low intracellular pH. It has been shown that the intracellular pH of various rat tumors is lower than that of blood (pH 6.948-7.193) (2). Hence PIPSE and MOSE are likely to localize in tumors providing that the intracellular pH is lower than 7.4. These compounds will be screened in various heterotransplanted human tumors in nude mice to determine their tumor localizing potential. To date only PIPSE has been studied in mice bearing transplanted primitive neuroectodermal (PNET) and neuroblastoma tumors. Anesthetized animals were injected into the retro-orbital venous plexus with the radiopharmaceutical. Animals were sacrificed at 4 and 24 hours post injection with the tumor and other tissues removed, weighed and counted in a scintillation counter. The relative concentration of the PIPSE in the tumor and other tissues was determined.

RESULTS AND CONCLUSIONS:

The preliminary results of this study are shown in Table 9. Because the tumor kinetics are not known, tissue data was collected at both 4 and 24 hours after injection. As yet there is not enough data to determine an optimal imaging time, i.e. when the tumor to blood ratio is maximized. The tissue data is very similar to that reported by Kung and Blau in the rat (1), that is, the activity is rapidly cleared from the blood. In addition, the concentration of PIPSE is initially high in liver, spleen, kidneys and lungs and then decreases by 24 hours. The concentration of PIPSE in brain is very high at 4 hours compared to other tissues but does not seem to decrease as rapidly by 24 hours as liver, spleen and lungs. As seen by the % total body retention, PIPSE is rapidly excreted. Rapid excretion is essential when using a long lived isotope like Se-75 ($T_{1/2} = 120.4$ d) in order to decrease the radiation dose.

The tumor concentration of PIPSE, from this preliminary study, is modest. The tumor to blood and tumor to muscle ratios are quite significant though.

In conclusion, this class of radiopharmaceutical holds promise for tumor localization. However, more distribution studies need to be performed in smaller, more viable tumors. In addition, more data needs to be obtained on the kinetics of this class of compounds in tumors in order to determine an optimal imaging time. The tumors surveyed to date were of neural origin, however, different types of tumors such as carcinomas and sarcomas will be looked at in the future in both nude mice in addition to spontaneous tumors in dogs. A comparison of tumor uptake of PIPSE will also be done with Ga-67 citrate.

TABLE 9

Se-75 PIPSE in Nude Mouse Relative Concentration

	4 hr				24 hr		
	Neuro- blastoma	Neuro- blastoma	PNET	PNET	Neuro- blastoma	Neuro- blastoma	PNET
Tumor	0.21	0.14	0.19	0.19	0.05	0.04	0.05
Blood	0.04	0.03	0.04	0.03	0.006	0.01	0.004
Muscle	0.16	0.06	0.06	0.06	0.01	0.01	0.007
Heart	0.08	0.07	0.08	0.06	0.02	0.01	0.01
Lungs	0.28	0.31	0.28	0.28	0.04	0.04	0.04
Liver	0.49	0.44	0.52	0.35	0.12	0.11	0.07
Spleen	0.42	0.26	0.47	0.51	0.05	0.04	0.03
Pancreas	0.58	0.41	0.39	0.43	0.08	0.06	0.05
Adrenals	1.52	0.51	0.76	0.39	0.20	0.12	0.03
Kidneys	0.42	0.31	0.33	0.33	0.10	0.13	0.07
Stomach	0.18	0.16	0.17	0.20	0.03	0.03	0.02
Intestine	1.05	0.93	1.17	1.14	0.06	0.05	0.08
Brain	0.89	0.76	0.72	0.56	0.36	0.39	0.33
Sal. Glds.	3.34	1.87	1.53	1.84	0.55	0.50	0.45
R. Eye (Inj)	0.36	0.32	0.54	0.82	0.11	0.16	0.03
L. Eye	0.35	0.26	0.21	0.21	0.05	0.05	0.04
Testes	0.58	0.21	-	0.23	0.09	0.09	0.10
Ovaries & Uterus	-	-	0.27	-	-	-	-
Tumor/Blood	5.3	4.2	4.6	6.6	8.5	6.4	12.1
Tumor/Muscle	1.3	2.4	3.3	3.1	4.3	4.5	7.0
Tumor wt(g)	5.8	4.7	3.2	0.8	4.9	10.3	2.9
% Total body retention	36.6	27.1	38.2	41.9	4.2	4.8	4.6

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11. METABOLISM OF ^{13}N -AMMONIA IN PORTACAVAL SHUNTED RATS

OBJECTIVE:

To understand the alterations in ammonia metabolism produced by portacaval anastomosis, as a means of furthering our understanding of such alterations in hepatic coma.

SCOPE OF INVESTIGATION:

Our experience has shown that studies of the gross distribution of label arising from injection of ^{13}N -ammonia in rats, when carried out for an extensive set of tissues and time points, yield highly useful information on the roles of the various organs and tissues in ammonia metabolism. A pilot experiment was performed in which adult male Wistar rats, 12 weeks after surgical construction of a portacaval shunt (at which time neuroanatomical abnormalities are known to occur), were injected intravenously with ^{13}N -ammonia under pentobarbital sedation, sacrificed at 5 intervals after injection and the ^{13}N content of 14 tissues measured.

RESULTS AND CONCLUSIONS:

The results of this experiment are shown in Table 10. In comparison with distribution studies of ^{13}N -ammonia carried out in normal rats and reported by us previously, a number of striking alterations in the patterns of ^{13}N tissue content were observed. (See also section 13 of this report for the 12 second distribution in normal rats).

Blood ^{13}N concentrations were higher than those in normal rats throughout the period of observation (0.2 - 40 minutes). At least for the early time points, this result is consistent with the known elevation of blood ammonia produced by portacaval shunting. While the 12 second ^{13}N relative concentrations in lung and heart were quite comparable to those of normal rats, suggesting that the fractional extractions for ammonia were unaltered, these organs released extracted ^{13}N much more rapidly than did the lungs and heart of normals. In the case of the lung, this may represent an elevated activity of glutamine synthetase. On the other hand, the kidneys, which also exhibited a 12 second relative concentration in the normal range, maintained ^{13}N concentrations considerably higher than normal between 2 and 40 minutes. In muscle, with the exception of the 20 minute relative concentration, which was within the normal range, the other measurements were well below normal. Whether this represents an increased rate of turnover, as appears to be the case with the lungs, or saturation of muscle ammonia-metabolizing capacity is a matter of considerable interest, since the musculature is thought to play a major role in ammonia detoxification. Liver ^{13}N concentrations were not very far from normal values, which suggests that increased arterial flow was, to some extent, compensating for the eliminated portal flow. The first three values shown for small intestine are 2-3 times normal, perhaps reflecting the altered blood flow (in addition to possible metabolic adaptation) produced by shunting. Finally, although the 12 second relative concentration of brain was below normal, the remaining values were above normal, particularly the 40 minute result. This may be associated with the known elevation of brain glutamine in shunted rats.

TABLE 10

Distribution of ^{13}N Following Intravenous Injection of ^{13}N -Ammonia in
Pentobarbital-Anesthetized Male Wistar Rats, 12 Weeks After Installation
of Portacaval Shunt

Time (minutes):	0.2	2	5	20	40
	<u>Relative Concentration</u>				
Blood	4.41*	1.49	1.04	0.573	0.629
Heart	8.55	3.99	3.20	3.92	2.87
Lungs	40.8	10.47	3.53	1.24	1.40
Liver	2.12	3.34	2.34	2.38	2.47
Spleen	3.17	6.97	4.93	1.59	1.50
Pancreas	3.72	6.14	5.39	3.54	3.12
Sm. Intestine (-contents)	8.05	5.39	8.35	2.06	1.63
Kidneys	16.9	15.4	10.2	4.91	4.45
Testes	0.184	0.563	0.403	0.987	0.829
Muscle	0.270	0.527	0.529	1.02	0.714
Submax. Salivary Glands	1.05	2.20	3.84	3.45	3.12
Skin	0.110	0.418	0.496	0.887	0.626
Calvarium	1.33	0.949	0.447	0.414	0.432
Brain	0.873	1.15	1.41	1.80	2.22
			<u>% Dose</u>		
Heart	2.73	1.60	1.17	1.34	0.797
Lungs	18.21	5.15	3.02	0.464	0.579
Liver	3.97	6.00	3.24	4.44	5.11
Spleen	0.854	1.65	1.31	0.261	0.599
Kidneys	12.11	12.97	11.01	3.47	2.97
Testes	0.0968	0.258	0.151	0.318	0.675
Submax. Salivary Glands	0.151	0.324	0.704	0.352	0.440
Brain	0.477	0.517	1.05	0.779	1.05
Whole Gut Tract	17.56				
*Collected Chest Blood	10.13				

12. ^{13}N -AMMONIA METABOLISM IN RAT LUNG

OBJECTIVE:

To understand the role of the lung in the metabolism of blood-borne ammonia.

SCOPE OF INVESTIGATION:

We have previously shown that intravenous injection of ^{13}N -ammonia in rats (pentobarbital-anesthetized) yields high concentrations of ^{13}N in the lungs at 0.5 and 2 minutes after injection. While most of the ^{13}N in the lungs and blood at 30 seconds was found to be unmetabolized ammonia, neutral amino acid(s) made up 30% and 22% of the ^{13}N in these tissues, respectively. At 2 minutes, neutral amino acid(s) constituted 73% and 52% of lung and blood ^{13}N , respectively, while 28% of blood ^{13}N was incorporated in urea. The lungs maintained a more than 30-fold concentration gradient, with respect to blood, of ^{13}N -labeled ammonia and neutral amino acid(s) at both 0.5 and 2 minutes. Breath collection showed that ^{13}N -ammonia in expired air amounted to, at most, a few ppm of the injected dose. These findings have been extended by additional measurements reported below.

RESULTS AND CONCLUSIONS

Lung ^{13}N relative concentration (% dose/% body weight) measurements were carried out at 6 and 12 seconds after intravenous injection of ^{13}N -ammonia in pentobarbital-sedated adult male Sprague-Dawley rats. The values obtained to date for the first 2 minutes after injection are as follows (mean $\pm$ s.e.m.): 6 seconds, 61.2 ± 4.0 (4); 12 seconds, 41.8 ± 6.8 (6); 30 seconds, 53.6 ± 7.5 (5); 2 minutes, 22.8 ± 5.0 (5). There was a considerable degree of overlap of the measurements at the first three time points and none of the corresponding means differed significantly ($p < .05$) from the other two by the rank-sum test (two-tailed). Gamma camera studies in two rats, however, indicated decreases of ^{13}N activity (decay-corrected) of approximately 30% in the lung region between 6 and 30 seconds after injection, which can be regarded as consistent with the above tissue data. The variability observed in the measured lung ^{13}N concentrations may reflect variations in cardiac output corresponding to varying levels of sedation. Since rat lung receives an extremely high rate of blood flow (approx. 40 ml/minute/g in pentobarbital-sedated rats), its extraction of blood-borne ammonia may be quite sensitive to changes in the rate of perfusion. Blood pH shifts arising from anesthesia-induced acidosis may also play a role.

The rapidity of systemic removal of ammonia from blood was apparent in measurements of the ^{13}N content of blood collected from the chest cavity after excision of the heart at 6 and 12 seconds after femoral vein injection of ^{13}N -ammonia. These collections, which, on average, amounted to 3% of the body weight (or about half the blood supply), contained (mean $\pm$ s.e.m.) 9.8 ± 1.1 (4) % dose and $5.57 \pm .58$ (6) % dose, respectively. The relative concentrations of these blood collections

were $3.32 \pm .18$ (4) and $1.82 \pm .21$ (6), respectively. The mean relative concentrations of arterial blood taken at 30 seconds and 2 minutes were $1.62 \pm .16$ (4) and $1.02 \pm .07$ (9), respectively.

To further resolve the ^{13}N -labeled neutral amino acid fractions previously reported for lung and blood, picric acid extracts of specimens taken at 2 minutes after injection were freed of picrate by passage through 0.5×0.5 cm columns of DOWEX-1 (acetate form). The columns were eluted with 0.4 ml of 100 mM sodium L-aspartate (to ensure removal of any residual amino acids from the columns) and the pass-through and eluate were incubated for 20 minutes (37C) with 250 μg of glutaminase. The glutaminase-treated solutions were then subjected to high-pressure liquid chromatography (HPLC), as described in reference 1. The ammonia fractions of the 2 minute lung and blood specimens thus treated were found to contain $93.7 \pm 1.6\%$ and $63.5 \pm 8.7\%$ (mean $\pm$ s.e.m., $n=3$) of total nonprecipitable ^{13}N , respectively. Subtraction of the ammonia fractions found for untreated specimens gave ^{13}N -(amide) labeled glutamine fractions of $69.2 \pm 2.7\%$ and $48.3 \pm 8.7\%$ for lung and blood, respectively. Subtraction of the previously determined ^{13}N -urea fractions from the residual (neutral amino acid + urea) peaks following glutaminase treatment indicated that other (unresolved) neutral amino acid(s) made up at most $2.4 \pm 1.1\%$ and $7.5 \pm 9.5\%$ of the 2 minute lung and blood nonprecipitable ^{13}N content, respectively.

Since published measurements of glutamine synthetase in rat tissues indicated no (2) or rather low levels (3) of activity in the lungs, the above results prompted us to undertake our own measurement. A γ -glutamyl-hydroxamate assay coupled with an ATP-generating system (A.J.L. Cooper - unpublished data) showed a rather high level of glutamine synthetase activity in the rat lung: 99 ± 9 $\mu\text{mol/g/hour}$ (mean $\pm$ s.e.m., $n=5$).

Additional evidence for de novo synthesis of glutamine in the lungs was obtained by removing the lungs at 6 seconds after femoral vein injection of ^{13}N -ammonia, in order to preclude uptake of labeled metabolites formed in, and released by, other tissues. Picric acid extracts of a portion of the lungs were subjected to HPLC, as before. Another portion was incubated for 20 minutes at 37C in 5 ml of Krebs-Ringer solution containing 5 mM glucose. At the end of 20 minutes, 2 ml of 1% picric acid was added, the lung specimen and solution homogenized at 0C, centrifuged, and the supernatant analyzed by HPLC. The results, presented in Table 11 show that, at 6 seconds after injection, about 25% of lung ^{13}N was already in the neutral amino acid fraction. Given our other experimental results, it must be concluded that the labeled species was glutamine. Further, incubation of lung excised at 6 seconds produced a significant increase in the metabolized fraction of total lung ^{13}N , with the main increase occurring in glutamine.

These studies are the first to demonstrate glutamine synthesis in the mammalian lung. The role of the lung in the metabolism of blood-borne ammonia, hitherto overlooked, may have important implications for disease states involving abnormal ammonia metabolism, a prime example of which is hepatic coma.

TABLE 11

Distribution of ^{13}N -Labeled Species in Rat Lung Excised at 6 Seconds After

Femoral Vein Injection of ^{13}N -Ammonia, as Determined by HPLC

(% of Nonprecipitable $^{13}\text{N}^*$, Mean $\pm$ S.E.M., n=3)

Ammonia + Basic	Neutral Amino	Acidic Components
<u>Amino Acids</u>	<u>Acids + Urea</u>	<u>(GLU, ASP, etc)</u>

Fresh Lung Specimen

74.5 $\pm$ .6

24.7 $\pm$ .6

0.83 $\pm$ .03

Specimen (From Same Lungs as Above) Incubated for 20 Minutes (37C)

in Krebs-Ringer plus Glucose (5 mM)

64.1 $\pm$ 3.7

32.5 $\pm$ 3.3

3.36 $\pm$ .46

(* >99.5% of total lung ^{13}N)

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13. METABOLISM OF ^{13}N -LABELED AMMONIA AND L-AMINO ACIDS IN NORMAL AND DISEASE STATES

OBJECTIVE:

To investigate the extraction, retention, metabolism and recirculation of ^{13}N -labeled ammonia and L-amino acids in tissue in normal animals and in cancer and other disease states.

SCOPE OF INVESTIGATION:

Our studies of the distribution of ^{13}N in rat tissues following intravenous injection of ^{13}N -labeled ammonia and L-amino acids have been extended by the addition of a 12 second sacrifice time for ammonia and L-glutamate. These measurements are useful in estimating the first-pass fractional extraction of these compounds in tissue and in detecting interorganal flux of these compounds and their metabolites at early times after injection.

RESULTS AND CONCLUSION:

The results of these measurements, in which the heart vessels were severed at 12 seconds after femoral vein injection of the ^{13}N -labeled compounds into pentobarbital sedated rats, are shown in Tables 12 and 13. It is seen that ammonia was cleared from blood considerably more rapidly than was L-glutamate. Extraction of ammonia by the lungs (the subject of a separate section of this report) was much greater extraction than of L-glutamate. This was also the case for brain, heart and abdominal muscle. On the other hand, the liver and submaxillary salivary glands took up appreciably more L-glutamate than ammonia. In the case of the liver, this was at least partly a consequence of the lower extraction of L-glutamate by the splanchnic organs (spleen, pancreas and gut). In comparison with published values of the distribution of cardiac output in barbiturate-sedated rats as determined by labeled microspheres (see reference 1, for example), the fractional extraction of ammonia by the kidneys and of L-glutamate by the salivary glands were approximately 100%. The percent dose value shown for ammonia-derived ^{13}N in brain, when corrected for the portion of dose retained by the lungs and compared with microsphere data for fraction of cardiac output to the brain, gives an ammonia extraction of about 40%, which is quite close to the value for cerebral ammonia extraction in barbiturate-sedated rats reported by Lockwood *et al.* (2). However, in comparison with microsphere data for the perfusion of muscle, the relative concentration for both ammonia and L-glutamate in abdominal muscle appear anomalously high, suggesting that the microsphere method may underestimate the blood flow to muscle.

TABLE 12

Distribution of ^{13}N in Rat Tissue Following Intravenous Injectionof ^{13}N -ammonia: 12 second sacrifice(mean $\pm$ s.e.m., n = 6)

Tissue	Relative concentration*	% Dose
Chest-Pool Blood	1.82 $\pm$ .21	5.57 $\pm$ .58
Heart	9.20 $\pm$ .53	2.60 $\pm$ .18
Lungs	41.8 $\pm$ 6.8	20.1 $\pm$ 2.9
Liver	1.45 $\pm$ .20	4.83 $\pm$ .73
Spleen	4.86 $\pm$ .95	1.20 $\pm$ .23
Pancreas	4.76 $\pm$ .61	
Sm. Intestine (-contents)	3.05 $\pm$ .42	
Kidneys	18.6 $\pm$ 1.7	13.6 $\pm$ 1.2
Testes	0.437 $\pm$ .063	0.443 $\pm$ .056
Abdominal Muscle	0.621 $\pm$ .094	
" Fat	0.499 $\pm$ .069	
Submaxillary Salivary Glands	1.76 $\pm$ .37	0.313 $\pm$ .063
Skin	0.401 $\pm$ .054	
Calvarium	0.345 $\pm$ .039	
Brain	1.048 $\pm$ .088	0.552 $\pm$ .042

* % Dose/% Body Weight

(Adult Male Sprague-Dawley Rats under Pentobarbital)

TABLE 13
Distribution of ^{13}N in Rat Tissue Following Intravenous Injection
of L-(^{13}N) Glutamate: 12 second sacrifice
(mean $\pm$ s.e.m., n = 6)

Tissue	Relative concentration*	% Dose
Chest-Pool Blood	4.53 $\pm$ .40	14.3 $\pm$ 1.2
Heart	3.80 $\pm$ .42	1.10 $\pm$ .13
Lungs	18.0 $\pm$ 3.9	7.8 $\pm$ 1.7
Liver	3.76 $\pm$ .34	12.08 $\pm$ .86
Spleen	3.22 $\pm$ .37	0.815 $\pm$ .088
Pancreas	3.48 $\pm$ .14	
Sm. Intestine (-contents)	2.64 $\pm$ .16	
Kidneys	15.78 $\pm$ .90	11.77 $\pm$ .76
Testes	0.455 $\pm$ .057	0.444 $\pm$ .048
Abdominal Muscle	0.429 $\pm$ .039	
" Fat	0.438 $\pm$ .051	
Submaxillary Salivary Glands	2.90 $\pm$ .31	0.501 $\pm$ .051
Skin	0.501 $\pm$ .078	
Calvarium	0.580 $\pm$ .053	
Brain	0.239 $\pm$ .011	0.125 $\pm$ .008

* % Dose/% Body Weight

(Adult Male Sprague-Dawley Rats under Pentobarbital)

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14. ^{18}F -4-FLUOROESTRADIOL AND ANALOGUES AS POTENTIAL AGENTS FOR DETECTING HORMONE DEPENDENT TUMORS

OBJECTIVE:

The purpose of this study is to synthesize ^{18}F -4-fluoroestradiol and specific analogues and to determine whether they will bind sufficiently with estrogen receptor positive-tumors to allow detection by scanning. Evaluation of ^{18}F -labeled estrogens of hormone dependent tumors will be carried out using spontaneous and transplanted tumor models in rats and dogs.

SCOPE OF INVESTIGATION:

Many mammary tumors are known to be estrogen receptor positive and this has prognostic significance in humans. The development of an estrogen derivative containing a gamma-emitting nuclide will provide a diagnostic agent for the management of patients with breast cancer and other endocrine related cancers. Experiments by us at the Estrogen Receptor Laboratory in Memorial Hospital (1) and by Utne *et al.* (2) have shown 4-fluoroestradiol to have comparable physiological activity to estradiol itself. As in the case of human breast tumors, about 50% of canine mammary tumors are hormone dependent. Therefore, it should be possible to determine in a limited number of experiments in dogs whether quantitative scanning techniques with a given estrogen can be of prognostic value relative to receptor content evaluation. Imaging of tumors or metastases which are subsequently proven to be estrogen receptor positive will be indicative of a potential diagnostic agent. Since the prostate has also been observed to take up and retain tritiated labeled estrogens in hormonal dependent tissue, ^{18}F -4-fluoroestradiol and analogues are potential agents for imaging the prostate and prostatic tumors.

^{18}F -labeled 4-fluoroestradiol and 4-fluoroestrone have been synthesized in our laboratory (3) using the Schiemann reaction (Figure 16) by an adaptation of the procedure of Utne *et al.* (2) for producing non-radioactive fluorinated estrogens. We have produced ^{18}F -4-fluoroestradiol with specific activities up to 0.15 Ci/mmol and have carried out tissue distribution studies in rats bearing transplanted prostatic tumors as described below. Palmer *et al.* (4) labeled these compounds by the Schiemann reaction with similar results and carried out tissue distribution studies in normal male rats (5).

Labeling efficiency in the Schiemann reaction is low and since the number of receptor sites in hormone dependent tissue is small, labeling these sites requires tracer quantities of drug with sufficiently high specific activity (100-1000 Ci/mmol) to allow detection by scanning.

RESULTS AND CONCLUSIONS:

During the past year we have been investigating methods for the production of ^{18}F -aryl fluorides with very high specific activity (see section 15 concerning ^{18}F -haloperidol). Meanwhile we have studied the tissue distribution of ^{18}F -4-fluoroestradiol (0.15 Ci/mmol) in a male Copenhagen rat (320 g) bearing a transplanted slow-growing hormone sensitive estrogen receptor positive R 3327H prostatic adenocarcinoma of spontaneous origin. The rat was injected intracardially with 6 μCi of the compound while under a light ether anaesthesia and killed at 30 minutes. High isotope concentrations were observed in the liver and in the duodenum. There was very low uptake in the prostate and in the tumor. Only 0.1% of the injected dose was observed in each case. This was probably due to the very low specific activity material used in this study. The compound was not defluorinated to any significant extent since less than 0.1% of the injected dose was detected in the femur.

During the next year, we hope to carry out animal studies with very high specific activity material. ^{18}F -aryl fluorides have been prepared from aryl triazene in very high specific activity by Tewson and Welch (6), and Widdowson *et al.* (7) have recently prepared non-radioactive 4-fluoroestrone via aryl triazenes. We are adapting this procedure to the synthesis of the labeled compound. Animal studies will be carried out in rats with DMBA-induced mammary tumors, in rats with transplanted prostatic tumors of spontaneous origin, and in dogs with spontaneous mammary tumors.

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Figure 16

15. SPECIFIC DOPAMINE RECEPTOR-BINDING RADIOLABELED NEUROLEPTICS: SYNTHESIS AND IN VIVO MEASUREMENT WITH ^{18}F HALOPERIDOL

OBJECTIVE:

The general purpose of this work is to develop methodology for quantitative measurement of receptor populations in vivo in humans. Dopamine receptor distributions are our first priority, primarily because the methods for synthesis of the required high specific activity are very similar to those used for preparation of ^{18}F labeled 4-fluoroestradiol (another receptor related compound) and we have developed an anhydrous H^{18}F precursor essential to "no-carrier-added" organic synthesis of ^{18}F -haloperidol and other related compounds. Later, we hope to use the understanding of neurotransmitter receptor systems to investigate the possibility of measuring "opiate-like" receptors for gaining a greater understanding of pain, especially that associated with cancer.

SCOPE OF INVESTIGATION:

Dopaminergic pathways appear to be involved in a number of important brain functions including control of movement, autonomic function and mental and emotional status. It is likely that alterations in the function of some of these neuronal pathways are involved in neurological and psychiatric disorders. Direct labeling of dopamine receptor sites by radiolabeled neuroleptics is desirable to study these receptors in living animals and humans. Such methods are potentially useful for measurements of the regional distribution and levels of receptors, and for revealing dynamic aspects of the modulation of receptor mechanisms. Specific binding of neuroleptic drugs to mouse brain in vivo has been shown to be saturable. For spiroperidol this occurs at 1-5 $\mu\text{g}/\text{kg}$ body weight. It will be necessary for us to improve our current methods (0.8 mCi/mg, 0.3 Ci/mmol) for synthesizing haloperidol in order to prevent a high level of non-specific binding. Specific activities in excess of 100 Ci/mmol are needed for in vivo positron tomographic imaging studies of the regional distribution of the high affinity dopamine receptors. A carrier free preparation would provide a theoretical yield of 1.7×10^6 Ci/mmol.

Concurrently with the effort to develop a no-carrier-added synthesis for haloperidol preclinical, animal experiments are planned.

RESULTS AND CONCLUSIONS:

The synthesis of ^{18}F -haloperidol using a Schiemann type reaction yielded products with low specific activity which were adequate for pharmacological studies but insufficient for receptor studies (1,2). The maximum possible radiochemical yield in the Schiemann reaction is 25% since only one of the four fluorine atoms of the tetrafluoroborate anion enters the aromatic ring, and, in practice, radiochemical yields are approximately 2-15%. Since labeling dopamine receptor sites requires specific activities of 100-1000 Ci/mmol for positron tomographic imaging studies, alternative methods of introducing fluorine-18 into an aromatic nucleus are required. A number of unlabeled aromatic fluorides

have been synthesized through decomposition of aromatic diazonium compounds obtained by diazotization of the corresponding amines in concentrated hydrogen fluoride and by treatment of an appropriate diazoamino compound with anhydrous hydrogen fluoride (3-6). The development of synthetic methods for the introduction of ^{18}F into an aromatic ring through a labeled fluorine anion rather than through a tetrafluoroborate anion would have great potential for producing "no-carrier-added" ^{18}F -aryl-fluorides.

We have synthesized ^{18}F -haloperidol by diazotization of the corresponding amine. In a preliminary experiment, no-carrier-added ^{18}F -haloperidol was produced in low radiochemical yields (less than 0.2%) by decomposition of the labeled diazonium fluoride salt of 4'-amino-4-(4-hydroxy-4-(4-chlorophenyl) piperidino) butyrophenone, as outlined in Figure 17. A target for the preparation of anhydrous H^{18}F , has recently been developed in our laboratory (7,8). Fluorine-18 with no-carrier-added was extracted from the heated target by purging with 10% hydrogen in helium. In a "no-carrier-added" type synthesis, utilizing this target, anhydrous H^{18}F was collected in dry acetonitrile in a polyethylene tube and added to a cold solution of 1 mg of the aminobutyrophenone in acetonitrile in a platinum reaction vessel. A solution of trifluoroacetic acid (TFA) in acetonitrile was added and the labeled salt was prepared by diazotization at 0-5°C by the slow addition of a suspension of sodium nitrite in acetonitrile. The reagents were in slight stoichiometric excess and the total reaction volume was less than 0.5 ml. After stirring for an additional 15 minutes at 0-5°C, the solvent was evaporated and the dried residue was decomposed at 145°C for 4 min. The pyrolysis product was dissolved in a small amount of chloroform and chromatographed on neutral alumina. The product was eluted with chloroform. The eluant was washed with water, dried over sodium sulfate, and evaporated to a small volume. The central fraction from the column gave a spot on silica gel thin layer plates (chloroform:methyl alcohol:concentrated NH_4OH , 96:4:1), which had the same R_f value as an authentic sample of haloperidol. The product was not visible under ultra-violet illumination. Its position on the plate was determined by autoradiography. A mixture of the product and haloperidol indicated that essentially all the activity was coincident with the authentic material. Autoradiography of the chromatogram detected the presence of impurities which we estimate to be less than 5%. The radiochemical yield in the process was 0.14%. As will be discussed below, acetonitrile does not appear to be the best solvent for reactions involving decomposition of diazonium salts. In a carrier-added synthesis, the labeled salt was prepared by diazotization (without TFA) of the aminobutyrophenone in a solution of H^{18}F and aq. 48% HF in acetonitrile. After evaporation of the solvents, the residue was dried over P_2O_5 before it was pyrolyzed. Purification as before gave a radioactive product which was detected by ultra-violet illumination and which had the same R_f value as an authentic sample of haloperidol. The product was scraped off the TLC plate and eluted with chloroform. The identity of the product was established by mass spectroscopy. The radio-chemical yield of ^{18}F -haloperidol in the process was about 0.01%.

The synthesis of no-carrier-added ^{18}F -aryl-fluorides from diazoamino compounds (triazenes) and anhydrous H^{18}F has been reported recently by Tewson and Welch (9-11). H^{18}F produced by the deuteron bombardment of a neon-hydrogen mixture is recirculated over a silver wool plug coated with cesium hydroxide or cesium carbonate to yield Cs^{18}F . ^{18}F -Haloperidol and spiroperidol were synthesized through decomposition of their piperidyl triazenes in an organic solvent with Cs^{18}F and methane sulfonic acid. In this procedure, the corresponding aminobutyrophenones were converted to diazonium salts and stabilized by reaction with piperidine. The piperidyl triazenes were dissolved in an organic solvent and the diazonium salts were regenerated with acid. The silver wool plug with the activity adsorbed onto it was added and the salt was decomposed at 120-130°C for 4-6 minutes. Radiochemical yields of the fluorobutyrophenones were low and have been shown to depend on the washoff of activity from the silver wool and on the organic solvent used in the reaction. Among the solvents used, the best yields were obtained with benzene (0.7%) and bromobenzene (1.3%). When acetonitrile or trifluoroacetic acid were used as solvents, yields were less than 0.1%. There was some indication that yields might be improved (15% or better) if H^{18}F was added directly to the reaction solution. This experiment is feasible with our target, and we are adapting this procedure (Figure 18) in our laboratory for the preparation of ^{18}F labeled haloperidol and spiroperidol.

^{18}F -Haloperidol (0.8 mCi/mg) was administered to dogs and Rhesus monkeys. Focal plane and transaxial tomographic imaging of the heads of these animals was carried out using a positron tomograph (the Cyclotron Corporation Model 4200). The camera mode was used to observe the dynamics of uptake during the first 70 minutes after IV administration of the drug.

In our dog studies, brain showed a 2.4 min uptake halftime that reached a plateau at 20 min with a much slower 25 hr. clearance halftime. The drug was found to be slowly eliminated from the dog's brain and its displacement from the brain was observed on administration of 1 mg of L-dopa (Figure 19). In contrast, no displacement was observed from the dog's snout (Figure 20) where dopaminergic receptors are not expected to be found. Twenty-three transaxial tomographic slice images 1 cm FWHM thick and spaced at 1.4 cm were taken of the dog's brain (Figure 21) and of a monkey's head (Figure 22) which verified the presence of activity within the brain and salivary gland regions.

Figure 17

Scheme for synthesis of ^{18}F -haloperidol by diazotization of the corresponding amine.

Figure 18
Proposed synthesis of ^{18}F -haloperidol.

Figure 19

F-18 HALOPERIDOL BRAIN

Figure 20

F-18 HALOPERIDOL SNOOT

Figure 21

Figure 22

16. SYNTHESIS AND EVALUATION OF ^{11}C -AMINO ACIDS FOR PANCREATIC IMAGING, TUMOR LOCALIZATION, AND REGIONAL AMINO ACID TRANSPORT MEASUREMENT: ALPHA-AMINOISOBUTYRIC ACID (AIB), DL-VALINE AND OPTICALLY ACTIVE ISOMERS

OBJECTIVE:

The purpose of this study is to synthesize (1- ^{11}C)-alpha-amino-isobutyric acid, DL-valine-1- ^{11}C and related compounds, to evaluate these compounds and optical isomers as potential tumor or pancreatic scanning agents, and for measurement of tumor and other organ amino acid transport rates.

SCOPE OF INVESTIGATION:

Carbon-11 labeled amino acids have significant potential as agents for tumor and pancreas visualization. There is clinical evidence that DL-(1- ^{11}C)-valine, DL-(carboxyl- ^{11}C)-tryptophan and L-(methyl- ^{11}C) methionine are useful as pancreatic scanning agents and may also be useful as tumor-scanning agents as well (1-6). There is clinical evidence that the synthetic non-metabolized amino acids (1- ^{11}C)-1-aminocyclopentanecarboxylic acid (^{11}C -ACPC) and (1- ^{11}C)-1-aminocyclobutanecarboxylic acid (^{11}C -ACBC) are of value as tumor scanning agents (1,3,7,8). We have synthesized (1- ^{11}C)-alpha-aminoisobutyric acid (^{11}C -AIB), another synthetic non-metabolized amino acid (9,12) in order to investigate its potential as a tumor scanning agent for brain and other regions of the body. AIB is distinguished by its failure to cross the blood-brain-barrier (9,13,14), and, therefore ^{11}C -AIB may be useful in assessing "blood-brain-barrier" permeability. In contrast, ACPC enters the brain at a rate approximately the same as that into other organs (11,12,15). Since AIB enters and concentrates in viable cells, high tumor-to-brain concentration ratios may be anticipated on "breakdown" of the blood-brain-barrier. An autoradiographic technique has been developed (16-18) to measure the blood-to-brain transfer of AIB across normal brain capillaries in rats. The permeability of tumor capillaries measured by this method in different tumor regions of rats with Walker 256 metastatic brain tumors ranged from 2 to 100 times as high as that of normal brain (13,14). AIB is incorporated rapidly into cells, and, since it is not metabolized further, it offers the possibility of studying amino acid transport into cells without potential interference by subsequent metabolic events.

We have made carbon-11 by the proton irradiation of nitrogen and converted it to H^{11}CN in amounts up to 1.5 curies. As described in previous progress reports (19), H^{11}CN in a modified Bucherer-Strecker synthesis was used to produce C-11-carboxyl-labeled alpha-aminoisobutyric acid (AIB), DL-valine and the optically active amino acids L- and D-valine. DL-valine has been produced in our laboratory in amounts up to 25 mCi, and used in biodistribution studies in rats and dogs. Pyrogenicity tests of this compound are in progress. Optical separation of ^{11}C -DL-valine was achieved in reactions catalyzed by the specific actions of D- and L-amino acid oxidases. Up to 4 mCi of

L- and D-valine and an equivalent amount of ^{11}C -alpha-keto-isovaleric acid were obtained in these reactions. Work is progressing on the development of this technique. It is anticipated that about 10 mCi of L- and D-valine will be produced. Our synthesis of ^{11}C -AIB and its biodistribution in a dog with lymphosarcoma has been reported (20,21). Further studies on the preparation of this compound and its biodistribution in normal and diseased animals is described in this report.

RESULTS AND DISCUSSION:

Our sequence for the production of ^{11}C -AIB labeled in the carboxyl group is shown in Figure 23. Radiochemical yields of 25-60% have been obtained. Total activities of 8-16 mCi of ^{11}C -AIB from 400-700 mCi of H^{11}CN have been produced in 70-90 minutes. Specific activities of 2.1-3.4 mCi/mg of ^{11}C -AIB have been obtained in reactions carried out with about 0.13 millimoles of unlabeled sodium cyanide. Assay of the product by thin layer chromatography, and by high pressure liquid chromatography revealed only one radioactive zone and showed the radiopurity to exceed 95%.

In a typical experiment, H^{11}CN is bubbled into a glass gas absorption column containing 1 ml of 0.005 N KOH. This solution (containing K^{11}CN) is drained through a stopcock at the base of the column into a stainless steel pressure vessel having an internal volume of 10 ml. The reaction vessel is charged with a mixture of 23 mg acetone, 72 mg $(\text{NH}_4)_2\text{CO}_3$, 6.7 mg NH_4Cl and 8.2 mg (0.13 mmole) KCN prior to introduction of the K^{11}CN . The closed vessel is heated rapidly to 2100-2300°C and maintained at that temperature for 10 minutes after which it is rapidly cooled. One ml of 6N KOH is then introduced and the vessel is again heated at 2100-2300°C for another period of 10 minutes. The cooled reaction mixture is filtered and then loaded directly onto a 1.5 cm diameter by 5 cm length prewashed AG 1-X2, 100-200 mesh, anion exchange bed in the hydroxide form. Anionic components, including ^{11}C -AIB are retained by the column while cationic and non-ionic components pass through. After washing repeatedly with distilled water (50 ml) the column is then eluted with 1 N HCl, the process being monitored by means of an ion chamber. This eluate (15 ml) is then loaded onto a prewashed 1.0 cm (diameter) x 15 cm (length) AG 50W-X2, 50-100 mesh, cation exchange bed in the hydrogen form. Cationic material (^{11}C -AIB) is retained while anionic material passes through the column. After being washed repeatedly with distilled water (50 ml), the column is slowly eluted with 0.2 N NaOH, the process again being monitored with an ion chamber to minimize the volume of eluate containing the product (10 ml). The purified ^{11}C -AIB solution can then be adjusted to physiologic pH with HCl and sterilized by microfiltration for investigational use.

The product gave only one spot on silica gel and cellulose chromatograms in two different solvent systems (N-butanol-water-acetic acid, 50:25:25 and N-propanol-0.1 N aq. ammonia, 50:50) which had the same R_f values as an authentic sample of AIB. Only one radioactive peak was observed on chromatography through a Partisil SAX HPLC column. The product was freed of salt (NaCl) by sublimation under vacuum. The

identity and chemical purity (> 95%) of the product was confirmed by spectroscopic analysis (nuclear magnetic resonance, chemical ionization mass spectrometry) of the sublimate.

Reactions are presently being carried out with lower carrier levels of sodium cyanide. A modified production method utilizing HPLC has been reported (22) which reduces the time required for synthesis and purification of ^{11}C -amino acids. This modification should be applicable to the production of ^{11}C -AIB and is presently being investigated. The chemical purity of the product will be further assessed after it is desalted through a AG-11G ion exchange retardation resin. Sterility and pyrogenicity tests of ^{11}C -AIB are in progress.

The distribution of ^{11}C -alpha aminoisobutyric acid (AIB) was measured in the tissues of healthy Copenhagen rats (see Table 14); in those with slow-growing, hormone sensitive, and receptor positive R3327H prostate adenocarcinoma (see Table 15); and with fast growing R3327G prostate adenocarcinoma (see Table 16). The tumor to prostate ratio in the slow growing rats averaged 2.8 without treatment and 0.7 with hormone treatment. This ratio for fastgrowing tumors was 2.2 without treatment and 0.9 with non-hormonal treatment. These data suggest the possibility of detection of prostate carcinoma and the evaluation of treatment success with ^{11}C -AIB. The relatively high uptake seen in surrounding tissue (intestines) and in blood makes this a highly tentative suggestion. The prostate to intestine and to blood ratios are much more favorable in the dog (see Table 14).

The results of tissue distribution studies in three dogs with ^{11}C -AIB are shown in Table 17. A 2.2 g nasal adenocarcinoma located in the nasal and brain cavities showed an extremely high relative concentration (9.7). This was a higher concentration than any tissue in the body except the kidney cortex which was 10.1. This tumor showed tumor to tissue ratios for blood, 21; brain, 30; liver, 3; intestines, 3; spleen, 6; kidney cortex, 1; and kidney medulla, 2. These results and the good, but moderate by comparison, values seen in the other two dogs, suggest this agent should be evaluated in humans for a variety of tumor types. We are particularly interested in the detection of tumors located in the brain where the blood to brain barrier will further aid in producing the high tumor-to-background ratios needed for detection of small tumors. Another area of interest is pancreatic imaging, since high concentrations were seen at all times in the rat (average 9.2 with a high value of 18.7 at 45 min) and in the dog (average 7.5).

The head of the dog with the nasal adenocarcinoma within the brain and nasal cavities was imaged using the Cyclotron Corporation Model 4200 Positron Camera-Tomograph (PCT). Figure 2 shows a 2-dimensional, tomographic, coronal, longitudinal focal plane image in antero-posterior/postero-anterior view. The adenocarcinoma and the various salivary glands in the head (parotid, submandibular and zygomatic) can be seen. As many as 23 slices 1.0 cm thick (full width at half maximum) and spaced at 1.4 cm can be reconstructed in a distance spanning 30.8 cm.

The slice positions are indicated at the edge of the 2-dimensional image. They are indexed on the rostral-caudal axis. The lower part of each slice image (Figure 24) is posterior and right is right so that they are viewed from above. The tumor is quantitatively viewed in slices a2, b2, and c2. These pictures demonstrate the capability of transaxial computed tomography to show the anatomical locations of activity concentrations without interference from over- and underlying activity. In addition, the differing structure seen in each adjacent slice emphasizes the importance of obtaining thin slices.

Synthesis of α - Aminoisobutyric Acid - I - ^{11}C

Figure 23

Figure 24

1 5 10
■■■■■■■■■■

TABLE 14

Distribution of ^{11}C -AIB in Healthy Copenhagen Rats

Tissue	Relative Concentration ($\frac{\text{dose fraction}}{\text{tissue weight (g)}}$)			Time (min)			body weight (g)
	15	30	45	45	60	90	
1. Blood	5.3	1.3	1.4	3.5	0.7	0.5	
2. Pancreas	5.8	11.7	18.7	9.0	6.0	4.2	
3. Kidney	7.3	6.2	24.6	8.9	10.3	5.1	
4. Intestine	1.5	2.7	7.2	4.0	2.4	2.0	
5. Stomach	0.7	2.0	5.9	2.2	1.7	0.3	
6. Thyroid	2.0	1.0	5.9	3.8	-	1.4	
7. Spleen	0.9	3.9	6.0	2.9	2.0	1.2	
8. Liver	1.1	1.2	3.3	2.2	1.7	1.3	
9. Lung	4.1	1.5	3.0	2.2	1.3	0.8	
10. Heart	2.8	0.8	2.3	1.9	0.8	0.8	
11. Bladder	0.4	0.7	2.1	2.2	1.0	0.4	
12. Prostate	0.3	0.5	1.7	1.4	0.6	0.6	
13. Muscle	0.3	0.5	1.0	1.5	0.5	-	
14. Testes*	0.4	0.3	0.7	0.8	0.3	0.2	
15. Epididymis	-	0.3	0.7	-	0.3	-	
16. Brain	0.2	0.4	0.6	0.6	0.2	0.5	

* Testes and epididymis

TABLE 15

Distribution of ^{11}C -AIB in Copenhagen Rats With
R3327 H Prostate Adenocarcinoma*

Tissue	Relative Concentration: $\left(\frac{\text{dose fraction}}{\text{tissue weight (g)}} \right) \cdot \text{body weight (g)}$								Hormone Treatment	
	No Treatment Time (minutes)		30	45	45	60	90		45	45
	15	15								
1. Blood	-	8.4	1.0	0.9	0.6	3.9	0.7		3.0	3.2
2. Pancreas	3.1	-	8.9	7.6	4.8	3.6	3.2		13.0	10.4
3. Kidney	1.2	5.1	7.1	5.7	9.2	3.5	3.4		3.5	6.9
4. Intestine	1.0	2.6	2.3	2.4	1.9	1.5	1.2		2.7	1.9
5. Stomach	0.5	2.2	1.5	2.1	1.1	0.6	0.8		1.3	2.3
6. Thyroid	1.0	1.9	3.7	3.2	3.9	-	1.2		1.6	3.5
7. Spleen	0.6	1.6	-	2.7	2.1	2.1	0.1		1.6	2.8
8. Liver	4.3	4.8	3.7	2.8	2.7	2.2	2.4		2.4	2.5
9. Lung	1.8	4.3	1.6	1.1	1.3	1.7	0.8		2.1	1.7
10. Heart	3.3	1.4	1.1	0.9	0.9	1.2	0.6		1.2	1.1
11. Bladder	1.0	-	-	-	0.7	0.4	0.4		3.0	1.0
12. Prostate	0.66	0.47	0.45	0.51	0.39	0.34	0.34		0.73	1.00
13. Muscle	-	0.95	0.29	0.28	0.36	0.55	-		-	-
14. Testes	0.56 ⁺	0.48 ⁺	0.32 ⁺	0.35 ⁺	0.24 ⁺	0.17 ⁺	0.21		0.38	0.51
15. Epididymis	-	-	-	-	-	-	0.34		1.16	0.56
16. Brain	0.65	0.09	0.19	0.23	2.37	0.12	0.03		0.26	0.18
17. Tumor	0.25	1.44	-	2.18	1.05	1.31	0.73		0.43	0.87
18. Necrotic Tumor	-	-	-	-	-	-	0.31		0.14	-

* Slow growing, hormone-sensitive and receptor positive

⁺ Testes and epididymis

TABLE 16

Distribution of ^{11}C -AIB in Copenhagen Rats with Fast
Growing R3327G Prostate Adenocarcinoma

Tissue	Relative Concentration $\left(\frac{\text{dose fraction}}{\text{tissue weight (g)}} \cdot \text{body weight(g)} \right)$					
	No Treatment			Non-hormonal Treatment		
	Time (minutes)					
	45	60	75	60	60	75
1. Blood	1.0	12.3	1.6	-	4.6	0.5
2. Pancreas	7.5	18.0	3.1	-	-	3.5
3. Kidney	10.0	22.0	5.1	5.4	4.5	6.3
4. Intestines	2.4	3.4	1.4	1.0	-	1.7
5. Stomach	0.5	4.4	1.6	-	-	1.1
6. Thyroid	3.8	3.2	-	10.7	1.6	1.6
7. Spleen	1.8	5.2	2.1	-	-	2.6
8. Liver	2.7	6.1	2.4	3.0	1.7	2.3
9. Lung	2.7	4.5	5.4	2.0	1.6	-
10. Heart	3.0	1.7	0.9	1.7	1.3	0.9
11. Bladder	1.0	1.2	0.4	1.2	0.6	0.4
12. Prostate	0.55	1.06	0.31	1.26	0.83	0.34
13. Muscle	0.60	-	0.31	-	-	-
14. Testes*	0.56*	0.44	0.17*	0.14	0.11	0.23
15. Epididymis	-	0.70	-	0.69	0.37	0.19
16. Brain	1.34	2.17	0.20	0.80	0.11	0.15
17. Tumor	0.95	3.32	0.51	0.61	0.56	0.54
18. Necrotic tumor	-	0.63	-	0.35	0.16	0.19
19. Fluid tumor	-	-	-	-	-	0.57

* Testes and epididymis

TABLE 17

Tissue Distribution of Alpha-Aminoisobutyric Acid (AIB) in Dogs with Spontaneous Cancer

	Adnexal Gland Adenocarcinoma (at 1.57 hours)	Lympho- sarcoma (at 1.41 hours)	Nasal Adeno- carcinoma (at 1.90 hours)
Pancreas	8.8	4.5	9.2
Intestine			
a. small clean	7.5	-	-
b. small w/feces	2.2	1.9	-
c. duodenum	-	2.2	2.9
d. jejunum	-	-	2.5
e. ileum	-	-	2.9
f. cecum	-	-	3.5
g. colon clean	1.9	2.3	3.1
h. feces	-	-	0.47
Kidney	-	2.0	-
a. cortex	4.5	-	10.1
b. Medulla	1.8	-	5.2
Liver	4.4	2.1	3.3
Salivary glands			
a. mandibular	3.0	2.2	4.7
b. parotid	1.1	1.6	-
c. zygomatic	-	-	7.5
Prostate	2.7	none	3.2
Esophagus (3 cm)	-	-	1.3
Trachea	-	-	0.82
Stomach (clean)	1.8	1.3	1.4
Gallbladder			1.5
Spleen	1.6	5.6	1.7
Myocardium	1.2	2.0	2.9
Bladder	1.2	0.9	5.9
Bone w/marrow	0.9	1.4	-
Testis	0.77	none	-
Eye	0.72	0.80	-

TABLE 17 (cont.)

Tissue Distribution of Alpha-Aminoisobutyric Acid (AIB) in Dogs with Spontaneous Cancer

	Adnexal Gland Adenocarcinoma (at 1.57 hours)	Lympho- sarcoma (at 1.41 hours)	Nasal Adeno- carcinoma (at 1.90 hours)
Lymph Nodes			
a. Neck	0.72	-	-
b. Cervical	0.55	-	-
c. Left popliteal	0.50	-	-
d. Right popliteal	0.17	-	-
e. Abdomen	-	-	6.9
f. Face	-	-	3.1
Thyroid	0.70	1.8	0.87
Pituitary	-	-	4.6
Adrenal Gland	0.58	1.2	1.8
Brain	0.55	0.16	0.31
a. cerebellum	-	-	0.38
b. brainstem	-	-	0.27
c. frontal lobe	-	-	0.35
d. R. cerebral hemisphere	-	-	0.29
e. L. cerebral hemisphere	-	-	0.30
Muscle	0.35	0.22	-
Fat	0.19	0.57	0.21
Uterus	none	1.3	none
Ovaries w/oviduct	none	0.89	none
Primary tumor	1.7	-	9.7
Tumor (Benign leiomyoma)	-	-	1.3
Lung	-	2.8	1.4
a. w/barely palpable tumor	1.8		
b. w/70% tumor	0.8		-
c. w/90% tumor	1.8		-
Lymph Nodes with tumor			
a. Mesenteric	-	3.2	-
b. Inguinal	-	2.8	-
c. Mediastinal	-	2.3	-
d. Submandibular	-	2.3	-

TABLE 17 (cont.)

Tissue Distribution of Alpha-Aminoisobutyric Acid (AIB) in Dogs with Spontaneous Cancer

	Adnexal Gland Adenocarcinoma (at 1.57 hours)	Lympho- sarcoma (at 1.41 hours)	Nasal Adeno- carcinoma (at 1.90 hours)
Whole Blood			
a. at sacrifice	0.70	0.67	0.47
b. at 1 hour	-	1.3	-
c. at 6 min	1.1	-	-
d. at 1 min	0.29	-	-

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17. CARBON-11-LABELED PRECURSOR COMPOUNDS

OBJECTIVE:

The development of a versatile, reliable, easy to operate system for the regular production of ^{11}C -labeled precursor compounds in sufficient yield to permit use of precursors in the synthesis of more complex radiochemical agents.

SCOPE OF INVESTIGATION:

The production of ^{11}C precursor compounds at this laboratory has been a continuing effort. A unified system to provide a number of ^{11}C precursors was designed and constructed to permit synthesis of H^{11}CN , H^{11}CHO , $^{11}\text{CH}_3\text{I}$ and $^{11}\text{CH}_4$ from $^{11}\text{CO}_2$. Dismantling or altering the apparatus when choosing one compound for preparation immediately following the preparation of another is unnecessary.

Carbon-11- CO_2 is produced by the proton bombardment of nitrogen containing one to five percent oxygen. No difficulties have been encountered with recovery of the activity and the conversion of $^{11}\text{CO}_2$ to H^{11}CN is routine. The ^{11}C -formaldehyde and ^{11}C -methyl iodide procedures are under continuing development. These simple compounds must be readily available to the synthetic organic radiochemist.

RESULTS AND CONCLUSIONS:

Seventeen experiments were performed, 4 of which involved use, repair, or improvement of the H^{11}CN system. Ten runs successfully provided H^{11}CN for the preparation of biologically interesting compounds. The runs made this year are summarized by the table below and shown with the 1978-79 summary for comparison.

SUMMARY OF ^{11}C PRECURSOR COMPOUND* OPERATIONS

	78-79	79-80
Synthesis of ^{11}C -labeled compounds for biologic studies	16	10
Apparatus testing (including repairs)	5	4
Pilot Studies	3	1
CN Development (chemistry)	4	1
Total ^{11}C precursor compound operations	<u>4</u>	<u>1</u>
	32	17

*Exclusive of ^{11}CO studies.

The number of runs attempted was roughly one half the number in the preceding period. During the report period, the yield of H^{11}CN was increased to 2.5 Ci at the end of collection of $^{11}\text{CO}_2$. From this 1.13 Ci of H^{11}CN was available for synthesis.

18. SYNTHESIS OF ^{18}F -PRECURSOR COMPOUNDS

OBJECTIVE:

To devise methods and hardware for the preparation of no carrier added ^{18}F for incorporation into fluorinated organic compounds.

SCOPE OF INVESTIGATION:

The proposed research was separated into four categories: 1) target development, 2) radiation chemistry, 3) post-irradiation processing, and 4) compound characterization. Work during this report period has concentrated upon target development and post-irradiation processing to remove ^{18}F activity from the target.

RESULTS AND CONCLUSIONS:

The choice of nickel as the material for construction of targets for producing F-18 by the reaction $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$ is largely based on the available data regarding the safe handling of fluorine and protection of apparatus from corrosion by fluorine. Metals are passivated to fluorine attack by forming the fluoride salt on the metal surface by reaction with fluorine. Available reports, which are studies of F for F exchange between H^{18}F and halogen fluorides or fluoromethanes indicate the absence of exchange between H^{18}F and passivated metals, but the most quantitative data states nothing other than the error to the experiments from the exchange reactions is less than 1%. The preparation of materials of biologic interest frequently demands the highest possible specific activities. For example, the use of ^{18}F -fluoroestradiol to study estrogen binding sites requires that the steroid not saturate available binding sites. It is necessary to obtain F-18 precursor compounds without dilution of the isotope. The use of a target passivated by reaction with fluorine is not consistent with the preparation of ultra-high specific activity ^{18}F . In this work F-18 is made by the irradiation of neon with deuterons by the $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$ reaction. As no fluorine is used in preparation of the target or apparatus, all fluorine produced will be F-18. Since the fluorine is so reactive, it is not normally detected in either the target neon or the material of target chamber construction.

One curie of F-18 corresponds to only about 3.3×10^{14} atoms of F-18, about 0.5 nmoles. Since the coating on the walls of a fluorine passivated target involves millimolar quantities of fluorine, losses as small as a part per million of the coating will cause isotopic dilution of the product. The number of ^{18}F atoms produced is small with respect to any detectable impurity in the gas and very small with respect to the number of sites available for reaction, absorption, adsorption, or other process which removes fluorine from the mixture with the gas phase. The first task in design of a target for the production of ^{18}F by bombarding neon with deuterons is finding the material which most readily releases ^{18}F to a selected purge gas.

The release of ^{18}F from a target chamber to a purge gas depends on several factors. Among these, the material of which the target is made and the selection of the purge gas are the most important. Criteria for the selection of the purge gas are compatibility of the gas with a wide range of solvents and use of simple, safe, rugged handling equipment. The gas chosen was 10% hydrogen in helium. Due to the lack of data regarding the retention of F-18 by metals and the difficulty of removing F-18 from an existing nickel target, experiments were undertaken to find what metals would most readily release F-18 to the purge gas. A frame to hold foil samples was constructed so the foils were held in the neon out of the path of the beam. The initial experiments used several readily available foil samples. One by twelve centimeter strips were arranged on the support rack so the major surface paralleled the beam axis and the rack placed inside a nickel target tube sealed at each end with nickel plates. After insuring the absence of leaks, the foils were treated by heating to 300°C while purging with 10% hydrogen in helium. The target was then filled with neon gas and irradiated with deuterons. Following irradiation the target gas was exhausted by purging with 10% hydrogen in helium and heating of the target to the preselected temperature. Aluminum was found to retain more F-18 activity than any other tested material. The activity distribution along the axis of the target was not constant and a suitable correction was made using aluminum strips to determine the variation. The foils were examined with a Ge(Li) detector and multichannel analyser. No peak other than the 0.511 MeV gamma photon from the positron annihilation radiation was observed, demonstrating that no activation of the foils occurred by direct contact with the deuteron beam. A value of activity retained per unit area of foil was derived and used to compare the various materials. These values are shown in Table 18.

TABLE 18

F-18 ACTIVITY RETAINED PER UNIT AREA FOR DIFFERENT PURGE TEMPERATURES

Arbitrary units normalized to aluminum = 100

<u>Final Purge Temp.</u>	<u>CU</u>	<u>NI</u>	<u>W</u>	<u>Mo</u>
Ambient	68	95	64	75
100°C	60	77	63	73
200°C	28	31	25	45
300°C	15	24	16	23

Based on these data copper was selected as the material of choice for the construction of a prototype target for the production of F-18 HF. A diagram of this target is shown in Figure 25. Several runs with this target have shown that the F-18 activity produced is easily removed from the target in reproducible amounts of 3.0 mCi per microamp following a one hour bombardment. Seventy-five percent of the total activity produced in the target chamber plus target gas is removable as F-18 activity based

on dose rate measurements of the target before and after removal of the F-18. It is believed that most of the residual activity is due to gallium and zinc activities induced in the Cu entrance window although precise determination is difficult due to inability to measure the whole target with sufficient accuracy.

A new (Mod. 1) target was developed with an entrance window consisting of a 2.5 mm thick plate with a hand-lapped seal to the target tube to clamp the foil in place. Operation of the new target involves initial preparation by purging the target while heating to 320°C. The target is stored with purge gas until use. For irradiation it is filled with neon to a pressure of 1.2 atm, closed, and irradiated in a static condition. After irradiation the target gas is exhausted to the atmosphere and the target purged while heating to 320°C. The purge gas passed directly from the target through a short insulated tube to a copper or polyethylene collection trap immersed in an ice-alcohol bath (-50°C) or liquid nitrogen. F-18 retained quantitatively in the trap distills out at about room temperature when the cooling is removed. KOH evaporated from methanol onto copper retains activity in the cooled trap. The F-18 activity on the KOH can be removed along with the KOH, by water or methanol. Polyethylene traps containing pyridine or N, N-dimethylformamide, acetonitrile, and cooled by immersion in liquid nitrogen also retain the activity. The activity is quantitatively recovered with the solvent from the trap after the trap is allowed to warm to room temperature. A sample of the activity trapped with pyridine followed a straight line decay for >1400 minutes with a half-life of 110.4 minutes. Examination of the entire samples from DMF, pyridine, acetonitrile and KOH collections with a Ge(Li) detector and spectrometer showed no detectable radioactive impurities. The identity of the compound as H¹⁸F was confirmed by synthesizing ¹⁸F-4-fluoro-estrone methyl ether via a Schiemann type reaction and ¹⁸F-haloperidol via the diazonium fluoride salt. The identity of these products was established by thin-layer chromatography and mass spectroscopic analysis. Based on these syntheses and the distillation of the activity near room temperature, the form of the F-18 and the distillation of the activity near room temperature, the form of the F-18 is identified as no carrier added H¹⁸F. Table 19 shows the average performance of the target which has been used at sustained beam currents up to 30 μ Amp. The Mod. 1 target has operated trouble free for over 15 consecutive cyclotron irradiations.

TABLE 19

ALL COPPER TARGET PERFORMANCE (AVG.)

<u>Target Type</u>	<u>Integrated Beam Curr.</u>	<u>Length of Irradiation</u>	<u>Yield mCi/μAmp EOSB</u>
Prototype	1 μ A hr.	1 hr.	9.4
Mod. 1	1 μ A hr.	3/4 hr.	11.2
Mod. 1	5 μ A hr.	1/2 hr.	11.1
Mod. 1	7.5 μ A hr.	< 1/2 hr.	9.8
		Average	10.1 $\pm$ 1.3

Figure 25

Prototype Copper ^{18}F Target

19. ENZYMATIC SYNTHESIS OF (N-13)-L-AMINO ACIDS

OBJECTIVE:

To synthesize L-(¹³N) amino acids enzymatically and to use these compounds in metabolic studies and as tumor and/or organ imaging agents in animal model systems and in clinical studies.

SCOPE OF INVESTIGATION:

During the preceding report period we had extended our clinical studies with L-(¹³N)-glutamate as a tumor imaging agent to a larger spectrum of tumors. Repeat studies were beginning to be carried out on patients who were undergoing chemotherapy to determine the efficacy of L-(¹³N)-glutamate uptake as an indication of response of the tumor to treatment. The preparation of L-(¹³N) valine for clinical studies was being developed.

RESULTS:

Clinical studies with L-(¹³N) glutamate were initiated in April, 1978. During the report period (Jan. 1, 1979 - May 30, 1980) 112 clinical experiments were carried out. The results of these investigations are discussed in detail in other parts of this report. L-(¹³N) Glutamate, in yields of 50-100 mCi, is synthesized from ¹³N-ammonia and α-ketoglutarate in a reaction catalyzed by glutamate dehydrogenase which has been immobilized on CNBr-activated Sepharose as a solid support. Limulus tests are conducted on the eluates of the immobilized column prior to use. Although the column retains its enzymatic activity, limulus tests of the eluate record positive results 3 weeks after preparation, suggesting bacterial contamination. We thus routinely prepare new immobilized columns every second week. To date no untoward reactions have been observed in patients receiving L-(¹³N) glutamate. Two sets of studies were cancelled because of positive limulus tests. In one of these studies the limulus kit gave false positive results. On a few occasions, the yields of L-(¹³N) glutamate were less than desired. This was a result of either low [¹³N]-ammonia production or poor enzymatic conversion to the labeled amino acid. Amounts as low as 2 mCi have proved useful for imaging studies.

A number of α-keto acids other than α-ketoglutarate are known to be substrates for glutamate dehydrogenase. Our initial attempts to synthesize L-[¹³N] valine from glutamate dehydrogenase immobilized on CNBr activated Sepharose resulted in low yields (1-5 mCi) which were not satisfactory for clinical studies. A detailed study was carried out to determine the optimum conditions for the synthesis of L[¹³N] amino acids from the appropriate α-keto acid in reactions catalyzed by glutamate dehydrogenase. Although the amino acid specificity of glutamate dehydrogenase has been extensively studied, apparently no detailed study of its α-keto acid specificity has been reported. In last years progress report the Km and Vmax of glutamate dehydrogenase were reported for a number of α-keto acids. Employing those parameters as a guide we have been able to use glutamate dehydrogenase immobilized on CNBr-activated Sepharose to synthesize apyrogenic preparations of radiochemically pure L-[¹³N] valine,

L- [^{13}N] methionine, L- [^{13}N] leucine, L- [^{13}N] alanine and L- [^{13}N] α -aminobutyrate from their respective α -ketoacids by modifying the reaction conditions from that used to prepare L- [^{13}N] glutamate from α -ketoglutarate. For example, to prepare L- [^{13}N] valine, the concentration of α -ketoisovaleric acid was increased to 72 μmol in 3 ml of glycine-KOH buffer, pH 9.0. This solution, which also contained 2 μmol of reduced nicotinamide adenine dinucleotide (NADH) and 100-200 mCi of [^{13}N] ammonia was added to a column containing 1 g of CNBr-activated Sepharose onto which glutamate dehydrogenase had been immobilized. This solution, whose volume was equal to the void volume of the Sepharose column, was kept in contact with the bound enzyme for 10 minutes before being washed through the column, with 3 ml of buffer. A yield exceeding 60% conversion of [^{13}N] ammonia to L- [^{13}N] valine was obtained in this manner with final yields of 15-30 mCi.

Clinical studies with L- (^{13}N) valine for tumor and pancreas imaging are now commencing. Pyrogenicity tests for L- (^{13}N) methionine have been completed and protocols approved for patients use for this compound as well as for leucine and alanine are in progress.

20. POSITRON EMISSION TOMOGRAPHY - REVIEW AND APPLICATIONS

A. SUMMARY EVALUATION OF PC 4200 TOMOGRAPHIC CAMERA

OBJECTIVE:

To carry out a clinical evaluation of the Model 4200 Positron Camera-Tomograph, and to perform clinical, animal and instrumentation development research studies.

SCOPE OF INVESTIGATION:

1. Clinical evaluation and research studies:

a. ^{18}F Sodium fluoride: A continuing program to evaluate the extent to which tomographic images enhance routine bone imaging with Na^{18}F has been investigated in a series of patient studies.

b. ^{11}C -Carbon monoxide: A number of patient studies were initiated to investigate the capability of the PC T 4200 in various body regions; e.g., head, throat, and limbs, for quantitative 2- and 3-dimensional static and 2-dimensional dynamic imaging procedures. The general clinical purposes of these studies include patient selection for chemical therapy (amount of circulating hemoglobin as a selection parameter) and for detection of tumor recurrence by means of serial studies in which changes in tissue vascularity are noted.

c. ^{13}N -L-Glutamate: Patient and human volunteers were studied to evaluate the normal and tumor-modified distribution of this agent.

d. ^{38}K -Potassium chloride: Patient and human studies were planned to begin the evaluation of this agent as a myocardial agent.

e. ^{11}C -carbon dioxide: A patient evaluation of this compound was initiated to determine its value as a tumor localizing agent.

2. Animal Research:

a. ^{11}C -AIB: Carbon-11 labeled alpha-aminoisobutyric acid has been synthesized for the first time and a series of imaging studies initiated in dogs bearing spontaneous tumors. This agent has potential for imaging primary and metastatic brain tumors due to a blood-brain barrier restriction of AIB into normal brain. In regions where the blood-brain barrier is broken down, viable cells accumulate and concentrate AIB. The agents currently used in Nuclear Medicine for brain scans, e.g., $^{99\text{m}}\text{Tc}$ -pertechnetate, do not enter cells once having passed the blood-brain barrier. The additional distribution space provided by cell entry and concentration, should provide extremely high brain to tumor activity concentration ratios. The ratio expected from ^{14}C -autoradiographic studies in mice will likely result in brain imaging with this agent becoming the method of choice for early detection of brain tumors.

AIB is transported with the general characteristics of small neutral amino acid (e.g., glycine, alanine, serine and proline) and therefore we expect it will be found of utility for in vivo studies of amino acid transport. The special transport characteristics into tumors may prove useful for diagnosis, and further changes brought about by means of chemical therapies may prove useful as monitors for the effects of therapy upon tumors and normal tissues. The non-metabolized characteristic of this agent will aid in the understanding of its in vivo distribution. Our initial success in finding positive and specific localization of this agent in lymphosarcoma suggests strongly continued evaluation of this agent.

b. $H^{11}CN$; Carbon-11 labeled hydrogen cyanide is being used to investigate its potential as a tumor localizing agent. It has been reported that $H^{11}CN$ may reflect gradients of oxygen consumption and energy expenditure in various physiological states, as well as in deviations induced by disease or drugs, and thus may be useful in assessing tumor metabolism.

c. ^{15}O Steady-state inhalation of O_2 , CO_2 , and CO : The value of serial studies of circulating red cells (^{15}CO), rapidly exchangeable water space ($^{15}O_2 \rightarrow H_2 + ^{15}O$), and molecular oxygen consumption ($^{15}O_2$) through and subsequent to radiation therapy treatment is being investigated in order to evaluate it as a monitor of the effectiveness of the therapy.

d. ^{18}F -Haloperidol: Because changes in the concentration of receptors are known to be brought about by disease in some in vivo receptor systems we feel an agent known to bind to dopamine receptors may be valuable as a pilot study of receptor alterations associated with brain functions.

3. Instrumentation Investigation:

We were concerned with the capability of the PC-T 4200 to produce quantitative images of the distribution of a positron-emitting radio-nuclide when in-coincidence gamma-rays other than the back-to-back 0.511 MeV positron annihilation gammas were emitted during the decay. Potassium-38 decays by 100% positron emission with a 99.8% 2.168 MeV gamma-ray in coincidence. Two kinds of background would be provided by the high energy gamma-ray:

a. True coincidence events not properly located, one 0.511 MeV and one 2.2 MeV gamma ray interactions providing the coincident events, similar to scatter events observed as a background in the usual operation of positron coincidence imaging instrumentation.

b. Events produced by detection of annihilation radiation derived from positron-electron pair production by the high energy gamma-ray in its interaction with the object being imaged as well as the shielding materials which are part of the positron imaging system.

RESULTS AND CONCLUSIONS:

The number and a brief description of the studies carried out using the Model 4200 Positron Camera Tomograph are presented in Table 20. Since Sept. 1, 79 there were 106 patient studies, 12 animal studies, and 2 instrument evaluations carried out for a total of 120 multiple image studies. Most studies included one transaxial tomographic measurement which provided 23 slice images and a variety of dynamic focal plane tomographic camera images of the isotope distribution within the subject:

1. Clinical research studies:

a. ^{18}F -Sodium fluoride: The results of 37 patient studies are presented in section 4 of this report (1).

b. ^{11}C -Carbon monoxide: The tomograph portion of this study has included 1 dog, 1 human volunteer and 53 patients. A report of this work is included in section 6 of this report (2,3).

c. ^{13}N -L-Glutamate: We have carried out three normal volunteer and three patient studies with ^{13}N -L-glutamate where the heart and pancreas were observed. Both 2-dimensional focal plane and 3-dimensional transaxial tomographic studies produced fine quality images of the heart and pancreas. A paper has been submitted for publication concerning this work (4).

d. ^{38}K -Potassium chloride: Seven patient and human studies have been carried out. A manuscript including the results of these studies has been prepared (5).

e. ^{11}C -Carbon dioxide: Fourteen patients have been studied and a report of these preliminary studies included in section 5 of this report.

2. Animal Research:

a. ^{11}C -Alpha aminoisobutyric acid: Five dog studies were carried out including three where tissues taken at necropsy were measured for their activity content. The high uptakes observed in tumors and in the pancreas in these and in other studies in rodents suggests this agent should be extended to patients for evaluation. A detailed discussion of these studies is included within another section of this report (2,6,7).

b. ^{11}C -Hydrogen cyanide: Five studies in dogs have been carried out which show a very high and persistent uptake within the stomach and probably the pyloric antrum. We expect to develop this agent for human use, since the stomach uptake suggests this agent is likely to have value for diagnosis and evaluation of gastric cancer and ulcers. We have also observed high uptakes in dogs for this compound in a breast tumor, an adrenal gland adenocarcinoma, and a bladder cancer. A lymphosarcoma showed no uptake. This tumor uptake data in dogs with spontaneous

cancers suggests this agent may have value for human tumor localization.

c. ^{15}O Steady state: A study carried out in a dog with a hemangiopericytoma is currently being analyzed. The dog was treated with radiation therapy and imaging was carried out at four times before, during and following treatment. Oxygen-15 labeled molecular oxygen, carbon monoxide and carbon dioxide were used. Transaxial computed tomographic studies were carried out using the Cyclotron Corporation PCT 4200. These studies are expected to allow a better understanding of the radial dependence of metabolism, tissue water content and vascular volume in tumors subjected to therapy.

d. ^{18}F -Haloperidol: A complete report of progress toward the preparation of "no-carrier-added" ^{18}F -haloperidol and the in vivo evaluation of this agent in animals with positron tomography is included in another section of this report (7,8).

3. Instrumentation Investigation:

A series of measurements have been carried out to evaluate the comparative quantitative characteristics of a pure positron emitter (^{18}F) and one that emits in addition a high energy gamma-ray in coincidence with the positron annihilation radiation (^{38}K). Three phantom arrangements were compared: first, a line phantom for resolution and uniformity measurements; second, a ratio phantom in which activities in measured amounts in approximate ratios of 10:5:4:3:1 were placed in a 2.6 cm diameter cylinders within a 20 cm diameter lucite cylinder; and a third phantom, designed to approximate the situation of a high heart uptake within the body. A bottle containing Na^{18}F and then ^{38}KCl in water solution was placed within a 35 x 35 x 20 cm rectangular water filled tank. In the heart phantom 18% greater coincidence counts were observed for ^{38}K than for ^{18}F . In the region of the phantom outside (with a 2 cm margin) the heart activity, a 260% increase in the average background was observed. The resolution degradation observed in the line phantom was 14%. The results of the above described measurements were prepared for inclusion in a presentation and a manuscript submitted to the American Society of Therapeutic Radiologists meeting held in Atlanta, October 23-28, 1979 (9,10).

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TABLE 20
 POSITRON CAMERA TOMOGRAPH
 STUDIES AIDED BY THE PCT 4200

Compound	Purpose	Number	
		8/8/78 - 8/31/79	9/1/79 - 6/1/80
Na 18F	Patient	29	37
11CO	Patient	13	41
13N-Glutamate	Patient	6	2
13N-Valine	Patinet	-	1
13NH4	Patient	1	-
11CO2	Patient	-	14
38KCl	Patient	-	7
38KCl	Animal	11	11
18F-Haloperidol	Animal	1	1
18F-Estrone	Animal	-	2
18F-Estradiol	Animal	-	1
11CO	Animal	1	-
3N-Leucine	Animal	-	1
11C-Valine	Animal	-	1
15O2, C15O2, C15O	Animal	5	-
H11CN	Animal	2	3
11C-AAIB	Animal	3	2
11C-BAIB	Animal	-	1
Na 18F	Phantom	4	2
38KCl	Phantom	3	-
		<u>79</u>	<u>127</u>

B. REVIEW OF POSITRON TOMOGRAPHIC INSTRUMENTS

OBJECTIVE:

The objective of this section is to review the design details for two commercially available positron-emission transmutation (PET) tomographic designs: ORTEC ECAT II, and the Cyclotron Corporation PCT 4500.

SCOPE OF INVESTIGATION:

The ECAT II is a single slice system; whereas, the Cyclotron Corporation PCT Model 4500 is a multiple-slice imaging unit. Two other companies have expressed to us their interest in designing and building total-body units according to our needs, but at present only have advanced designs for small-bore/neuro units available. These companies are Scanditronix of Uppsala, Sweden and Atomic Energy of Canada Limited (AECL). Our continuing review of available total-body tomographs will include analysis of commercial units as well as continuing analysis of the design characteristics of units built and developed by various non-commercial laboratories (e.g. Donner Labs, U.C. Berkeley; Montreal Neurological Institute; and Washington University, St. Louis).

ORTEC has been manufacturing nuclear instrumentation modules and systems for over 20 years. Their experience in analyzing state-of-the-art electronics for nuclear research is extensive. As a basis for the ECAT, ORTEC started by using a proven PETT III design developed by the St. Louis group. They upgraded the computer configuration to a standard well-defined multi-user system, upgraded the mechanical design, and developed a standard modular electronic package (1). The ECAT II (2) reduced the system time resolution to 12.5 nsec from 25 nsec by employing constant fraction discriminators on all channels. The detection and electronic processing allow coincidence rates of up to 100,000 counts/sec with dead time losses of $\leq 2\%$. A high resolution, high sensitivity system employing bismuth germanate detectors is currently under development.

The basis for the first Cyclotron Corporation positron camera tomograph was the prototype PC II developed by Dr. Gordon Brownell at the Massachusetts General Hospital. The PCT 4200 (3) uses the original PC II design with improvements and modifications in the mechanical design of the gantry, the electronic hardware, and the computer system (the PC 4200 is currently on loan to MSKCC for clinical evaluation from the King Faisal Hospital and Research Center, Saudi Arabia). The PC 4500 proposed design as currently designated consists of four circular planes of 128 detectors each. The computer central processor will be a Digital Equipment Corporation (DEC) model PDP 11/60 with 67 Mbyte disk and an array processor for rapid image reconstruction. This system is multi-slice and incorporates cylindrical bismuth germanate detectors (4).

RESULTS AND CONCLUSIONS:

The comparative technical specifications of the two currently available total-body transaxial computer tomographic instruments are summarized in Table 21.

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TABLE 21

SUMMARY OF CURRENTLY AVAILABLE POSITRON TOMOGRAPH SPECIFICATIONS

SPECIFICATION	ORTEC: ECAT ^{TM} II (measured Specifications)	CYCLOTRON CORPORATION: PCT4500 (design Specification)
Number and arrangement of scintillation detectors	One bank of 66 NaI(Tl) detectors arranged hexagonally	Four rings of 128 Bismuth Germanate crystal detectors on 90 cm diameter
Crystal dimensions	Each crystal cylindrical, 3.8 cm wide x 7.5 cm deep	Unspecified
Intercrystal spacing	Crystals are 45.7 mm apart center therefore 7.6 mm separate adjacent crystals	2.2 cm center to center
Interplane shielding	1.5 inch of lead outside of detector plane	6 mm thick x 19 cm deep lead septa 2.5 cm. lead collars, front & back.
Number of planes along z axis	One slice will be imaged	Four straight across, 3 cross plane, total
Provisions for changing shielding configuration	Shadow shields, which define the spatial resolution are changeable	None
Field of view	50 cm field of view, with detector faces 100 cm apart	43cm diameter without "wobble", 45 with "wobble" with detector faces 90 cm apart on a circle
Patient opening	50 cm patient opening	50 cm wide x 40 cm high
Detection motion	Detector banks translate in 8 steps of 0.57 cm or 4 steps of 1.14 cm and rotate in 5° , 10° steps	16 point wobble on 20 mm diameter circle; rotation; z axis sampling by computer control couch motion.
Angular measurements	Angular samplings are made in 2.5° segments	Fully programmable

TABLE 21

SUMMARY OF POSITRON TOMOGRAPHY SPECIFICATIONS (Contd.)

SPECIFICATION	ORTEC: ECAT II	CYCLOTRON CORPORATION: PCT4500
Minimum time required for complete scan	10 seconds live time (minimum)	a. Full sampling, 1 cm FWHM, 30 sec. b. "on the fly", 1.4 cm FWHM, 5 sec. c. rotate only, 2.2 cm, 1 sec. d. stationary cross plane only, 2.2 cm, 0.25 sec.
Resolution characteristics (in the plane)	17.0±1.0 mm without shadow shields 13.5±1.0 mm with standard shadow shield 11.0±1.5 mm with high resolution shadow shields	High resolution: 1.0 cm FWHM on axis increasing to 1.5 cm FWHM at 22.5 cm radius. Medium resolution: 1.4 cm FWHM on axis, increasing to 1.9 cm FWHM at 22.5 cm radius.
Sensitivity characteristics	Slices number 1 and 2 have efficiency of >8,000 c/sec/μCi/ml @ High resolution shields; ≥ 12,500 c/sec/μCi/ml @ medium resolution shields; ≥25,000 c/sec/μCi/ml @ shields removed.	16,000 CPS/μCi/cm ³ (straight across plane) 22,000 CPS/μCi/cm ³ (cross plane) 1.3 x 10 ⁵ CPS/μCi/cm ³ (total system) with 20 cm diameter water filled phantom.
Z axis resolution	Without shadow shields, 18.5 mm±1.0 Standard shadow shields, 19.5mm±1.0 High resolution shadow shields, 20.5 mm ± 1.0 The measured nonuniformity of slice thickness across the transaxial plane is ≤ 1.0 mm.	Straight across 1.0 cm FWHM at center increasing to 1.5 cm FWHM at 22.5 cm radius. Cross plane: 1.0 cm FWHM at center increasing to 1.9 cm FWHM at 22.5 cm radius.
Count rate capability	Measured 90,000 cts/sec where 24% are randoms for one straight across slice at low resolution with 2-3/4 μCi/cm ³ .	2x10 ⁶ system coincidence counts/sec where 50% are random with 5μCi/cm ³ uniformly dispersed in a 20 cm diameter H ₂ O phantom.

TABLE 21

SUMMARY OF POSITRON TOMOGRAPHY SPECIFICATIONS (Contd.)

SPECIFICATION	ORTEC: ECAT II	CYCLOTRON CORPORATION: PCT4500
Resolution in 2 dimensional rectilinear mode	with standard shields and high resolution reconstruction approximately 15 mm, other choices at user's option	1 cm FWHM
Coincidence time resolution	$2\tau = 12.5$ nanoseconds	$2\tau = 25$ nanosec timing
Random coincidence correction	Three modes, operator electable: A) Increment totals, ignore randoms. B) Increment totals, decrement randoms C) Increment totals, route randoms to separate memory	Singles counting and delayed coincidence decrement
Type of discriminator	Constant fraction	Leading edge type with built-in noise rejection
Computer manufacturer/model No.	DEC PDP 11/60, RSX-11M	DEC PDP 11/60, RSX-11M and RT-11
Special processor		Array processor for rapid C.T. reconstruction analogic AP 400
Memory	128K MOS Memory (standard)	128K bytes MOS memory 67M byte drive and controller for data acquisition
Mass Memory		TJE 16 9 track magnetic tape & controller
Price (estimate)	\$ 495,000 F.O.B. Oak Ridge, Tenn.	\$1,603,715*
Delivery Time (estimate)	6-9 months ARO	1 year ARO

* Price escalation included in quotations
# 8000 - 812

21. PRODUCTION OF RADIONUCLIDES AND LABELLED COMPOUNDS IN REGULAR USE

OBJECTIVE:

To provide radionuclides as needed for regular use.

SCOPE OF INVESTIGATION:

The goal of the basic research program here is production of radionuclides, either in ionic form or incorporated into compounds, of demonstrated clinical utility. To achieve this goal, once the procedures to produce a given isotope or compound have been developed, requires regular and repetitive production of radionuclides with sufficient purity and reliability to permit the performance of clinical and biological studies.

RESULTS AND CONCLUSIONS:

Fluorine-18 produced by the irradiation of water with $^3\text{He}^{++}$ has been the most widely used radioisotope at this laboratory since its development in 1968. Over 110 runs at up to 3 batches (Avg. 100 mCi) per run were made during the report period. In addition 28 runs were made to provide ^{18}F for labelling experiments.

Nitrogen-13 is produced here by the proton bombardment of water, using the $^{16}\text{O}, (p, \alpha)^{13}\text{N}$ reaction. Over 100 runs of multiple batches per run were performed to produce ^{13}N for use in labelling amino acids or other biological purposes.

The production of ^{52}Fe for Hematological studies continued at an increased rate: 25 runs were performed as compared to 11 in the previous report period.

Twenty runs involving use of ^{11}C precursors were performed. Each run involved the production of three or four batches in many instances. It is usual practice to make H^{11}CN for the production of ^{11}C -AIB and for use directly as H^{11}CN in biological studies. The average batch of H^{11}CN provides about 750 mCi H^{11}CN to the chemist for synthetic use. Batches up to 2.1 Ci at the end of collection have provided as much as 1.33 Ci for further work.

In addition to ^{11}C precursors, 48 runs using ^{11}CO and $^{11}\text{CO}_2$ were made for the purpose of studying the potential use of these gases as indicators of response of tumor to therapy.

Oxygen-15 as $^{15}\text{O}_2$, C^{15}O , and C^{15}O_2 was used on nine occasions for animal studies. Measurements of the dose rate from the Hot Atom Transfer System were made with these labeled gases.

Eighteen runs were performed to produce ^{38}K . The average yield was about 15 mCi/Batch. Many of these runs required the preparation of several batches to exploit one of the principal advantages at ^{38}K : Its 7.6 minute half life allows studies to be repeated at about one to one and one-half hour intervals.

Altogether over 345 runs were performed for the routine production at radioisotopes.

22. HOT ATOM TRANSFER SYSTEM (HATS)

OBJECTIVE:

To provide rapid, reliable, safe transport of cyclotron produced radioactive materials to three remote clinical sites.

SCOPE OF INVESTIGATION:

When the cyclotron was installed in 1967, a 6 mm O.D. plastic tube connected the radioactive gas processing system in the cyclotron vault to the hood in the warm lab, one floor above and fifty meters laterally away from the cyclotron. This system operated until 1979. Labeled material in liquid or solid form was carried by hand in shielded containers to the place of use. The loan of a PC 4200 Positron Tomograph to the Biophysics Laboratory by the builder, The Cyclotron Corporation, Berkely CA., and the owner, the King Faisal Hospital of Saudi Arabia, as well as planned clinical investigations required the installation of a system for the rapid delivery of short-lived isotopes, both in liquid and gaseous forms.

RESULTS AND CONCLUSIONS:

The Hot Atom Transfer System (HATS) was designed to transport radioisotope preparations in solid, liquid or gaseous form from the cyclotron to the scanning facility at the cellar level of Kettering Laboratory to the Diagnostic Radiology Suite on the second floor of the Clinical Office Building and to the Nuclear Medicine Suite on the second floor of Howard Laboratory. The last two locations are on the opposite side of East 68th Street from the Kettering Laboratory where the cyclotron is located. A tunnel under East 68th street connects Kettering Laboratory to the Clinical Office Building. The HATS consists of two major units, the gas transfer tube (GTT) and the pneumatic transfer system (P-Tube). A drawing (Figure 26) shows the location of the areas involved and the route of the HATS.

The P-tube is a commercially supplied system specially modified for use here. Four inch (nominal) welded galvanized pipe connects each terminal directly with the sending station in the cyclotron facility counting area. A standard transmission cannister, called a "Rabbit", is blown through the pipe by air supplied from blowers in each station. Installing individual blowers in each station is less costly and easier to service than a central supply with diverter valves and return pipe. Prior to construction there was some concern that a rabbit may be jammed in the system in an unknown location. An electronic tracking system at the cyclotron terminal monitors the progress of the rabbit in transit. Transit times for the P-tube are: 1) to the scanning facility, ~ 5 seconds, 2) to the Diagnostic Radiology Suite, ~ 20 seconds, 3) to the Nuclear Medicine Suite, ~ 45 seconds. This compares to walking times of 15-30 seconds, 45 to 60 seconds, and 90 to 120 seconds, respectively.

The GTT connects to the radioactive gas processing system in the cyclotron "Hot Lab" and is led up to the cellar level of the Kettering Lab where it branches to the SKI scanning facility. Paralleling the route of the P-tube, the GTT passes through the tunnel under 68th street to a shaft rising to the second floor. A branch is led into the neuro-angiographic suite. The GTT then passes directly to the Positron Tomograph Room of the Nuclear Medicine Suite. The total run of the pipe is 170 meters of 316 stainless steel tube, 3 mm ID, 4.75 mm OD, inside a 3.8 cm OD PVC plastic pipe. The inner steel tube is joined with 316 stainless steel swagelok connectors throughout. Inspection ports were installed at appropriate points to allow any required maintenance. Each terminal consists of a locking stainless steel box with a quick-disconnect and flow control valve. The GTT was designed to operate at a concentration of 20 mCi of a pure positron decay radionuclide per liter of gas. The closest proximity to the line an individual will pass is the tunnel under East 68th Street. Figure 27 shows a cross section of the tunnel and the dose rates at one foot and one meter from the GTT, with 10 mCi ^{150}I flowing. A "worst case" calculation assuming that the system were operating 8 hour/day, 200 day/yr., is that an individual making thirtytwo leisurely 12 second trips through the tunnel every day would accumulate 2.7 mR/yr from this source. Selected to provide flow rates of 2 to 4 l/min at pressure differentials of 5 to 10 psig, the tubing diameter allowed for many bends and some possible restriction of flow which would result if any joints were left with flashing or the tube were crimped. A measured flow rate of 5.9 l/min at a 10 psi pressure differential shows the tube was installed with few flaws. The system volume is estimated at 1550 ml. For steady-state ^{150}I studies the usual primary gas flow rate is one liter/min, at a pressure drop of ~ 2 -3 psi. The average transit time at these conditions is 93 seconds, or just slightly less than the half life of ^{150}I . Higher flow rates and shorter transit times are possible. It is also possible at the cyclotron hot lab to pre-mix the gas with other gases to make an inhalation mixture. The increased delivery volume will decrease transit times even further. Modifications of the facilities to permit mixing of the gases, and analysis of the gases before dispatch to the site of use has begun. The H-P 5750 gas chromatograph was moved to the counting area of SCI and connected with suitable solenoid valves to the GTT. A vent to waste was installed to permit the adjustment of flow rates and concentration without flowing activity unnecessarily. Mixing valves to permit the addition of breathing mixtures or diluting gases were installed. Lines connecting the valves with the diluent gas supplies are not yet installed, but the manifold is in place.

The cyclotron communication system was extended to provide voice communication between the cyclotron console-counting room area with the Nuclear Medicine Facility and the Diagnostic Radiology Neuro-Angiography Suite. The connection to the warm lab was rewired at the same time to improve the voice quality of the system.

Figure 26

FIG 27 CROSS-SECTION OF
TUNNEL UNDER 68TH ST.

23. RADIATION EXPOSURE SUMMARY

The annual cumulative whole body γ and x - radiation exposure of individuals participating in this contract are summarized in Fig. 27. Not tabulated here are six individuals (secretarial staff, etc.) who have no exposure to radionuclides and do not enter areas where radionuclides are handled. We have endeavored to keep whole body exposure of individuals below 500 mR, far below the standard upper limit of SR. We feel we have succeeded moderately here, where 17 individuals were at or below 500 mR/year but 5 individuals above that but below 1200 MR/year.

PERSONNEL RADIATION EXPOSURE REPORT

Jan. 1, 1979 - Dec. 31, 1979

Figure 28

24. CYCLOTRON RESEARCH AND DEVELOPMENT

OBJECTIVE:

To maintain and improve cyclotron operating efficiency and reliability, to improve personnel and equipment safety and protection and to simplify and standardize cyclotron operation.

SCOPE OF INVESTIGATION:

The research programs utilizing the Sloan-Kettering cyclotron demand a high degree of cyclotron reliability and versatility, especially when patient scheduling is involved.

Cyclotron scheduling normally requires daily particle changeovers, and frequently twice daily or tri-daily changeovers, followed by cyclotron retuning at a different beam current. The limited particle energy of our cyclotron requires long term stable high and low beam currents for production of some isotopes and neutrons. To meet those demands we have concentrated on developing simple and standard cyclotron operation and maintenance methods, stable and reproducible beam currents, optimum extraction efficiencies and extended life time for perishable components.

RESULTS AND CONCLUSIONS:

A. The following projects, described in our 1979 Report, have been completed.

1. A Carbon Puller Modification to Reduce Replacement Cost: A modified carbon puller arrangement has been tested in routine use since Nov 1978 in the cyclotron (Fig. 33). The "plug" portion is eroded by the ions emerging from the ion source and needs replacement once a month at a cost of 6¢. By comparison, 6 pullers were replaced between Nov 77 and Nov 78 at a cost of \$675. The plug is cut from stock rod and enough material is on hand for 77 years.

This modification has resulted in an unanticipated benefit. The ion source anode is also eroded by the ions emerging from it and needs replacement twice a year. Resistance to heat conduction across the mating surfaces of the plug and puller body causes the plug to erode about twice as fast as the corresponding portion of the old puller. Some of this material is deposited on the face of the anode surface where the ions emerge, coating it with a heat resistant carbon surface. The anode, normally eroded by the emerging ions and needing replacement about twice a year, has not been replaced since March 1979 and shows little wear at present.

2. Rebuilding Our Damaged Ion Source: The inoperative ion source, part of the original equipment of our cyclotron, has been rebuilt and tested. After some initial problems with clogged water lines and vacuum leaks, the ion source was put into service and has been in routine use since March 1979.

Being water-cooled in a vacuum, this type of ion source is difficult to repair, thus having a spare on hand assures us of continued operation should one ion source fail.

3. New Internal Probe for Beam Monitoring: Assembly, testing installation and troubleshooting our new internal probe has been completed. Parts for this project have been available for some time, but other duties and projects had deferred its completion. This probe was designed to replace the original equipment for two reasons:

a. Increased internal beam currents due to improvements in cyclotron performance made here exceeded the cooling capacity of the original probe. The evaporated or sputtered copper generated by overheating caused vacuum problems and RF shorting in the dee box.

b. A set of adapters was needed when using the original probe since the probe transport equipment had previously been modified to accept the larger diameter of our internal target probe.

Due to these difficulties, the internal target probe was routinely used as a beam current monitor by installing a blank copper target disc, designed here by us to dissipate the heat caused by high beam currents. However, the internal target probe became moderately radioactive due to continual use and exposed personnel mounting the target to a 200 mR/hr field 6 in. from the probe head and at least 2,000 mR/hr for 30 sec. when remounting the blank.

The new probe has been in routine use since March 1979. The internal target probe is being used only for internal targets which are run no more than once a week, permitting the probe to "cool off" substantially between runs.

The new probe has been designed to map the beam orbit pattern using a second monitoring terminal that will accept fine pickup wires.

4. Internal Probe Carriage Extension: A radiation hazard was created when our internal target probe was built. The range of the mechanism which moves the probe in and out of the dee box was extended, but only enough to drive the probe into the dee box one inch less than extraction radius if the probe was to be withdrawn completely from the dee box, as when retrieving an irradiated internal target. For purposes of RF system troubleshooting the vault door interlock can be bypassed with a special key, if the probe is at its "in" limit, and the cyclotron turned on. The rationale was that the probe would stop the beam at low energy orbits if the ion source was also on, greatly reducing the severity of an accidental radiation exposure. Until now, the beam was stopped at high energy orbits. Extending the carriage a second time provides enough travel so that the probe can be sent in 7.9" less than extraction radius, where the beam is $\sim 15\%$ of maximum energy for any particle.

5. Operator Training: Personnel changes and the increased need for co-ordination of the cyclotron schedule with patient availability has placed heavy emphasis on training additional cyclotron operators from our staff. We have completed the training of four operators, which is sufficient to meet our immediate needs.

6. Spare Deflectors Modification: Our two spare and previously unusable deflectors have been modified so that the gap (extraction channel) between the negative electrode and grounded septum can be varied externally from outside the dee box. The deflector currently in use has this system.

This modification eliminates the great difficulties inherent in fixed-gap deflector operation when protons are run. Since proton extraction requires an extraction channel E-field gradient of about 300V/0.001 in., and the channel must be at least 0.220" wide to physically accommodate the He-3 beam, such a channel must be operated in excess of 65kV during proton operation. This condition required hour-long deflector baking in periods before proton runs and resulted in frequent arcing during the runs. The deflector also had to be removed frequently for cleaning. But the proton gap need only be 0.165" and the necessary E-field can be maintained with a much more manageable 55kV.

Maintenance of our one usable deflector involved large (1 rad) whole-body exposures for each of the two people performing the maintenance. Cooling of over a weekend was useless due to the long lives of the isotopes present in the deflector (Zn-65, etc.): Deflector maintenance presently must now be performed every 12 to 18 months. Having three usable deflectors allows each to cool off two to three years before being worked on. The present deflector in use is overdue for removal.

7. Faraday Cup Troubleshooting and Operation: This unit, funded as project 3005044 in late 1979 and assembled in late 1971, has not operated satisfactorily until today. Since the staff expressed little interest in its use, its completion was given low priority until recently when we experienced a sudden increase in the frequency of internal target irradiations.

The procedure for internal target irradiations calls for tuning the beam externally so that the optimum orientation of the beam in space is obtained to insure an even distribution of the beam across the target. Otherwise, yields are low and the target ablates due to local heating.

Difficulty arose on Wednesdays when F-52 and ^{11}C are run, that day being an ideal day for both because of scheduling. Setting up the ^{11}C target the night before was an important time saver for the time-consuming ^{11}C -patient studies on Wednesday, but the target, with its foil windows, should obviously not be used for tuning a high beam current irradiation such as needed for Fe-52 generation. Low current external He-3 beam tuning may be done with care, followed by high beam current irradiation internally, but the technique requires experience and skill, and the results are not always satisfactory. Also, there is always the risk of generating unwanted radionuclide species in the target. Because of this, and with proposals for new internal target usage, I felt the Faraday Cup's time had come.

The Faraday Cup assembly consists of a disc with two large holes near its outer diameter and spaced $\sim 90^\circ$ apart. At rest, the beam passes through one hole. Upon activation from the control console, the disc, driven by a rotary solenoid, brought the second hole, in which the Faraday Cup is mounted, into the beam line, and the disc was locked in place by a linear solenoid. The cup is water-cooled by two flexible metal hoses, which coil somewhat as the cup is rotated into place and provide the torque necessary for rotating the cup out of the beam. This equipment is mounted in a vacuum chamber. The problem was that the disc would not lock in place. I had thought that the rotary solenoid was not powerful enough, and since it was the most powerful on the market, a redesign of the cup was necessary. The difficulty was that it was too powerful! The disc overshot the locking mechanism before it could lock. Repeated activation of the rotary solenoid in attempts to have it lock only overheated it, causing it to lose power and not drive the disc to the locking mechanism. An appropriately placed bolt now acts as a stop to prevent overshooting, and a lead counterweight, located on the rim of the disc where it provides maximum torque counteracting that of the coiled water hoses when the cup was activated, now aids the tired solenoid.

B. The following project is currently being pursued.

1. Inner Orbits Correction: The quality and quantity of the internal beam and its effect on extraction efficiency and external beam depends on the configuration of the first turn and subsequent inner orbits, which in turn depend heavily on the positioning of components of the central region: the ion source, puller, first turn shield and dees. These parameters are a compromise between those necessary for maximum proton, He-3, He-4 and deuteron operation. A system of harmonic coil magnets are used to alter the phase space of the beam entering the deflector and are an important component of the external beam extraction system. Similar sets of coils installed close to the inner orbits of our cyclotron will increase extraction efficiency substantially by providing "tuning" ability of the inner orbits, thereby alleviating the negative effects of the compromise central region setup. Increased extraction efficiency will also lessen deflector loading, lengthening the period between servicings and thus reducing cyclotron staff radiation exposure levels. We have completed the design, fabrication and

installation of three sets of inner coils and have purchased the necessary power supplies. The control circuit for this project is being currently built and completion of the project is expected within six months.

C. The following projects have not been completed for the reasons stated.

1. Magnetic Channels Limiter: Installation of electromagnetic limiting devices on each end of our movable magnetic channels to prevent their damage and loss of calibration will be made after the Inner Orbit Coils Project is completed.

2. Target Current Limiter: An adjustable target current limiter interlocked with our cyclotron power to prevent target destruction will be installed upon completion of our Inner Orbit Coils Project.

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MEDICAL AND METABOLIC STUDIES WITH CYCLOTRON PRODUCED RADIONUCLIDES

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