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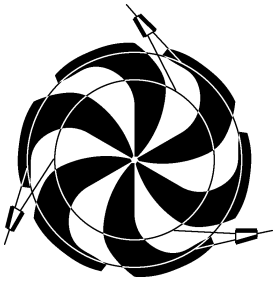

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UNDER A CONTRIBUTION FROM THE
NATIONAL RESEARCH COUNCIL OF CANADA

DECEMBER 2003

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LIFE SCIENCES

Introduction

The use of clinical PET reached a critical point within Canada, and in Vancouver in particular, this past year. The TRIUMF Life Sciences program has played a large role in bringing this technically challenging imaging modality from the research bench to the bedside. During this past year TRIUMF supplied the Cross Cancer Centre (CCC) at the University of Alberta with ^{18}F over a 9 month period (125 shipments) that enabled the Centre to begin its research and clinical program in the use of PET in the diagnosis of cancer. Locally, the supply of the radiotracer FDG was drawing to an end as the Vancouver Hospital prepared to take over this task and MDS Nordion showed interest in becoming more involved in the supply of PET tracers.

The applications of radiotracers for various projects at UBC continued to play a significant part of the program with the addition of radiochloride isotopes for visitors from the University of Toronto. Possible new tracers utilizing metallic isotopes will expand the already significant array of radiotracers available for the research PET at UBC. Plans are under way for expanding the facilities available for the Life Sciences program in the next 5 year plan.

Experiment LS0
PET facilities

(K.R. Buckley, TRIUMF)

The PET facilities comprise the TR13 13 MeV H^- cyclotron, the ECAT 953B/31 tomograph, and ancillary equipment such as counting and data acquisition systems.

Personnel

Carolyn English left for maternity leave this fall and a part time technologist (Hosien Kamrudin) has been hired to work Fridays. Caroline Williams will work extended hours Monday to Thursday to cover the scanning day and Hosien will work on Fridays. This allows us to continue operating the extended days required to accommodate our scanning protocols though it is dependent on the good graces of our technologists to keep up with the workload.

Dr. John Wilson from the Cross Cancer Institute in Edmonton stayed with us until the summer, learning cyclotron operation and carrying out the irradiations for the production of ^{18}F for shipment to Edmonton. Following John's departure, the Cross Cancer Institute sent Wayne Logus for the summer for training and to continue the irradiations. Wayne returned to Edmonton at the end of summer when their cyclotron began operations.

TR13 cyclotron

Usage of the TR13 cyclotron increased significantly this year in both runs conducted and delivered beam due to the irradiation of two high dose lithium targets for the production of ^{7}Be (LS8), the irradiation of a palladium target for ^{110m}Ag (LS8) and the routine supply of ^{18}F to the Cross Cancer Institute in Edmonton. The total number of runs increased to 1038 vs. 848 last year and delivered beam doubled to 1,258 mA min from 631 mA min.

Downtime this year was caused by two rf system problems and a cooling water leak under the cyclotron. These repairs required several days to complete. The cooling water leak resulted in the failure of the cryohead drive electronics in the compressor due to a poorly made splice to an electrical cable that ran in the vicinity of the water leak.

Nine extraction foil changes were required through the year and all targets where rebuilt at least once. Four ion source filament changes have been done along with other miscellaneous service items.

Presently there are six target locations occupied of the available eight. These consist of

- one ^{18}O-O_2 gas target
- one ^{18}O-water target
- one ^{16}O-water target
- one N_2/H_2 gas target
- two experimental gas targets.

A number of irradiations took place this year in support of LS8. The lithium target was operated twice this year, both times at 50 μA. One run was performed in early January for approximately 60 hours and a second run was performed in May for just over 100 hours. It is anticipated that that was the last run required.

We have been operating the niobium body gas target for the production of ^{14}O. This is the same target body we use for the production of fluoride from ^{18}O gas. We did another irradiation of an iron foil for production of ^{56}Co for calibration of the 8π detector in ISAC, and we irradiated another palladium foil for production of silver isotopes ^{110m}Ag for Brian Turrell in UBC Physics.

A fumehood was situated beside the TR13 cyclotron this summer to aid in development of ^{14}O production. The ^{14}O, with a half-life of 70 s, is recovered from the target in the form of H_2O. It was found to be too difficult to achieve this transport to the chemistry labs approximately 50 m away.

ECAT tomograph

Block detector failures and programmable array logic chips continue to be the dominant modes of failure for the camera. We are routinely repairing blocks in-house and have replaced 7 blocks again this year. We have still not assembled the necessary components to properly calibrate the blocks prior to returning them to the scanner. At present only a simple visual balance of PMT outputs is performed on the bench and the block set-up routine in the scanner performs the fine tuning. Programmable logic chips in the buckets continue to fail. Chips for nine channels have been replaced this year.

The array processor in the front end for 2D reconstructions had to be replaced again this year. A replacement was purchased from Byar's Consulting for a much better price than the last unit obtained from CTI.

A high voltage power supply was obtained to replace a drifting supply for the PMT high voltage. TRIUMF Electronics has not been able to isolate a fault in the original supply though the camera stability improved with the replacement of the supply. There is still a lingering drift in the ECAT calibration which is larger than the camera exhibited in previous years. We have been unsuccessful in determining the cause of this, however, it simply means that a calibration is performed more often to maintain the camera in allowable limits.

The ^{68}Ge transmission rods and uniform calibration cylinder were replaced this year with sources purchased from Sanders Medical.

Renovations in the UBC hospital have been completed for the installation of the HRRT from CTI. This new scanner will be installed in the space previously occupied by the original PETTVI scanner. This allows both the ECAT and the HRRT to be operated from the same control room. Delivery of the camera is expected early in 2003.

A small animal PET camera has also been purchased from Concorde Microsystems and is due for delivery in April, 2003.

Statistics

Table XI. ECAT scanning statistics.

		2002	2001
Total scans conducted		383	379
Total scans lost		37	52
Lost to	– patient	8	10
	– cyclotron	16	8
	– chemistry	3	6
	– scanner	7	13
	– staff sick/away	0	9
	– investigator	3	6

Table XII. TR13 run statistics.

		2002	2001
Total runs conducted		1038	848
Total runs lost		16	8
Total beam delivered (μA min)		1,258,376	631,357
Delivered to	– LS2	–	160
	– LS 3	301,611	262,573
	– LS 4	40,411	55,327
	– LS 8	605,500	14,4199
	– LS 13	51,410	33,611
	– LS 24	17,246	33,172
	– LS 32	240,995	91,240
	– LS 33	–	477
	– LS 39	1203	4580
	– LS 47	–	300
	– LS 49	–	3282
	– LS 52	–	2436

Experiment LS3
Synthesis of radiopharmaceuticals for positron emission tomography
(M.J. Adam, TRIUMF)

Daily routine production of up to 11 radiopharmaceuticals is currently performed with 3–4 radiophamaceuticals synthesized on any given day. FDG continued to be sent once per week to each of Vancouver, Lions Gate and St. Paul's Hospitals for research in cardiology and oncology. Out of these 11 radiopharmaceuticals, five (FDOPA, Raclopride, TBZ-OH, SCH23390 and MP) are used most heavily. There has been an increase in the number of Raclopride preparations from last year, making Raclopride the most heavily used radiopharmaceutical. Most of the Raclopride preparations this year are for the "Scatchard Analysis" experiment that Doris Doudet is performing on monkeys. These experiments require 3–4 Raclopride preparations each day where one is at high specific activity (5–10 Ci/μmol) and the others have carrier added to give a range of SAs of 2–35 Ci/μmol at time of injection. All preparations for these experiments are assayed by HPLC prior to injection to confirm the specific activity. There was a total of 642 production runs in 2001 for CIHR/PET and external users with 412 radiopharmaceutical syntheses carried out just for the TRIUMF/UBC PET Program.

The demand for FDG for our group remains low. However, most of our FDG production is being used by Lions Gate, St. Paul's and Vancouver General Hospitals for studies in oncology and cardiology (details in LS13, 24, 40, 48, 49 proposals). We currently send FDG to these hospitals one day per week in an amount

enough for imaging approximately 3–4 patients. Vancouver General Hospital is setting up an FDG synthesis system and the plan in the future is to send only ^{18}F-fluoride to Vancouver General Hospital and they will make the FDG for themselves and for all other local hospitals.

One of the main reasons for the large increase in the total production runs this year was the increase in shipments of ^{18}F-fluoride to Edmonton to three days each week for clinical cancer imaging (see LS32 proposal). The Cross Cancer Centre in Edmonton sent a chemist/trainee (Dr. John Wilson) to TRIUMF for a few months to carry out these runs and to learn cyclotron operations and PET chemistry. MDS Nordion handled the airline transport and Edmonton is paying all the transportation costs and the cost of the ^{18}O-water used in the target. The Cross Cancer Centre was able to carry out 5–6 patient scans with each shipment of radiofluorine from TRIUMF.

This year the preliminary experiments, carried out by Dr. Chong, using ^{11}C-PMP to study dementia in Parkinson's disease and diffuse Lewy body disease were completed. Previous studies in postmortem brains have shown that choline acetyltransferase activity, but not muscarinic cholinergic receptors, was markedly reduced in PD, diffuse Lewy body disease and Alzheimer's disease, and that neocortical cholinergic deficits correlate with severity of dementia in PD, diffuse Lewy body disease and Alzheimer's disease. As reduced cholinergic activity in the neocortex correlates with marked neuronal loss in the nucleus basalis of Meynert, these observations suggest that loss of cholinergic neurons in the basal forebrain may play a significant role in the pathogenesis of dementia in PD and diffuse Lewy body disease as well as in Alzheimer's disease.

This project has now been put on hold pending the analysis of data and the success of submitted grant applications.

The synthesis of ^{11}C-Carfentanil was successfully completed this year and will be ready for human use early in 2003. Dr. de la Fuente previously demonstrated, for the first time, that there was a measurable increase in the amount of dopamine released into the synapse when a placebo was administered, thus showing a chemical basis for the placebo affect. We now want to extend this research to look at other receptor systems that might be involved such as the opioid system. As with most new radiopharmaceutical projects, the synthesis of the precursor was the most labour intensive part.

The synthesis of ^{18}F-labelled oligonucleotides has also been started this year to compliment the Antisense research that has been ongoing in Dr. Stoessl's lab. To start, we tried repeating the procedure of the INSERM French group and are attempting to attach a fluorinated aromatic group to the phosphorothioate end of the above oligo. We demonstrated that we can attach the non radioactive label to the oligo and purify it on HPLC. However, attempts to synthesize the ^{18}F-labelled version have proven to be somewhat problematic. Unfortunately, it requires a multistep synthesis where the ^{18}F is introduced in the first step, making the procedure very difficult to carry out. We are attempting to find alternative, simpler methods to the ^{18}F-labelling of these oligos.

We continue to use TBAF in most of the ^{11}C methyl iodide reactions to enhance and stabilize the yields. We are fortunate to still obtain the nitro precursor of Setoperone as a gift from Jannsen Pharmaceuticals. We also are grateful to ASTRAZENECA AB for the gift of Raclopride Tartrate, used as carrier for the Scatchard experiments, and dihydroxy Raclopride as the precursor for labelling.

The separation of ± DTBZ into its active enantiomer was also achieved this year. We began imaging with the +, active enantiomer in 2002 and the images are much clearer without the significant background image created by the inactive isomer. We are currently comparing both images from the active isomer and the racemic mixture before completely converting to the active isomer.

Experiment LS4
TR13 targets for PET radioisotope production

(T.J. Ruth, TRIUMF)

Progress for 2002

At this stage we have the targets required for our PET program, namely a target to produce ^{18}F-F_2 and ^{11}C-CH_4. These two tracers represent starting material for the bulk of our radiopharmaceuticals. We have built back-up targets to reduce the downtime associated with window failures and target cleaning. However, they have not been installed as of this time due to scheduling. Because of a failure of our Ti water target in 2000, we redesigned the target and built it from niobium. This new target material has performed exceedingly well. Results were reported at the 8th Workshop on Targetry and Target Chemistry (WTTC), Turku, Finland in May, 2002.

^{18}F-fluoride system

Following on our experience with the stainless steel target, we wanted to build a target system capable of producing multi-curie quantities of ^{18}F-fluoride while being able to recycle the target material.

Methods

We have reported our work on a gas target system to produce ultra-high quantities of ^{18}F-fluoride at the WTTC and in the literature using a stainless steel target body. While these results demonstrated proof-of-principle concepts, there were improvements to be made around the efficiency of ^{18}F extraction from the target walls and the chemical reactivity of the ^{18}F-fluoride. Since that time, we have designed another gas/liquid handling system and other target bodies.

Our experience with a niobium bodied water target led us to use niobium for the target we report on here. Three features, in addition to material, separate this target from the previous designs: i) cartridge heaters mounted in the target body, ii) vent port at the rear of the target, made possible by the change in the water jacket design, and iii) zero dead-volume fittings in the target body.

The design of the gas and liquid handling system for this target is also different than that used previously. The key feature is the use of a heat trace and insulation around the transfer lines to and from the target. This allows the lines to be dried quickly and efficiently and may also aid in the transfer of the fluoride.

The transfer lines were constructed by wrapping two 3 mm O stainless steel lines together and wrapping this assembly with the heat trace. The heat trace was assembled by feeding Chromel-A heater wire through a 1.6 mm O teflon tube 5 m long, the Chromel-A wire is 5.417 Ω/m, yielding a total resistance of 34.7 Ω. The entire assembly was wrapped in standard plumbing insulation sleeves. Operating the heat trace at 48VAC results in 66 W which warms the transfer lines to approximately 75°C.

To conduct an irradiation, the target is first evacuated to a pressure less than 200 m torr by a mechanical vacuum pump. The target is then loaded by opening the 95% ^{18}O-O_2 reservoir to the target. The fill pressure is approximately 2060 kPa (300 psi). After the irradiation the O_2 is cryotrapped back to the reservoir with only small losses. The reservoir is 25 ml volume and the target is 24 ml volume. While the gas is being recovered (5 minutes) the target cooling water is shut off and the target and transfer lines are heated to 80 ± 5°C.

The mechanical vacuum pump is then used to evacuate the target which is next opened to a reservoir of HPLC grade water. The temperature on the rear of the target can be seen to drop 5°C when the target is full. The water is left in the target for 5 minutes before being pushed by 140 kPa (20 psi) helium over the ion separation column (Waters QMA Sep-Pak for example). The wash volume is approximately 50 ml.

A second target rinse is performed by partially evacuating the target with the mechanical pump and drawing a second volume of water into the target. Again, this is left in the target for 5 minutes before being pushed over the ion separation column. At this point in our work the column is removed and counted in an ion chamber or attached to an FDG synthesis module.

To dry the target in preparation for the next irradiation the target and transfer line heaters are left on at 80°C while helium at 140 kPa (20 psi) flows through the system. To determine that the system has dried, the mechanical pump vacuum pump is used to evacuate the system. The system is assumed dry when a pressure of less than 200 m torr can be obtained. In our tests, the time until the target was deemed dry and ready for the next irradiation was approximately 2 hours but no effort was made to determine the minimum time required.

Results

This target performs at near theoretical levels to 25 μA and with decreasing production rate for higher beam currents. Up to 50 μA, the higher beam current outweighs the loss of target thickness from density reduction to result in a net increase in yield. A 2 hour irradiation at 13 MeV and 50 μA yields 130 GBq (3.5 Ci). The ^{18}F-fluoride recovered from the target is equivalent in reactivity to that obtained from conventional targets irradiating ^{18}O-H_2O.

Conclusions

A gas target for producing ^{18}F-fluoride has been demonstrated to operate at 50 μA with the possibility of even higher beam currents which would result in extremely high production rates.

There are 2 patents pending for this system.

^{11}C-CH_4 production

Our previous work on static irradiations of a H_2/N_2 target gas for the production of methane indicated that recoverable yields at 13 MeV plateaued at about 750 mCi at EOB. The relatively poor yields were attributed in part to hot atom interactions with the target chamber walls. In order to try and overcome this limitation, an aluminum bodied flow-through gas target was implemented and tested for the production of ^{11}C-CH_4 on the TR13 cyclotron at TRIUMF. Nitrogen gas with varying quantities of hydrogen has been used to investigate the optimum ratio for methane production. Comparison of the flow-through target with the static-target irradiations for production of methane are given.

Methods

Aluminum body gas targets were designed with cylindrical bores of 12.7 mm ID and 120 to 127 mm lengths. A water-cooled support grid with 34 × 1.59 mm holes arranged in a hexagonal pattern with

1.78 mm between centres supported aluminum target window foils 25.4 μm thick. Transmission through the grid was calculated to be approximately 70%. Beam transmission studies indicated 64% transparency. Mixtures of N_2 with up to 20 percent H_2, pressurized up to 3.1 MPa were used to make ^{11}C-CH_4. For comparison, ^{11}C-CO_2 was produced in the same target system with a mixture of N_2 and 0.5% O_2, pressurized at 0.69 to 2.28 MPa. Gas flow in each case was 200 to 600 ml/min. Irradiations of up to 32 μA lasted up to 60 minutes. The radiolytic production of ammonia could be a concern for post production processing, e.g. ^{11}CH3I synthesis. To measure the ammonia thus produced we passed the target gas through a series of HCl traps and back-titrated to a phenolphthalein end point.

Results

Testing of the flow-through target gave a saturation yield of up to 2.89 GBq/μA (79 mCi/μA) ^{11}C-CH_4 at 32 μA with a correction for the grid transmission (both beam current on target gas and saturation yields). For comparison, ^{11}C-CO_2 was produced with a saturation yield of 2.66 GBq/μA (73 mCi/μA) at 27 μA with correction for grid losses. Yields did not improve above approximately 10% H_2. The maximum ^{11}C-CH_4 produced after a 35 minute run at 30 μA was 57.3 GBq (1.55 Ci). Preliminary measurements of the specific activity (SA) via the synthesis of ^{11}C-raclopride indicate that the EOS SA is approximately 13.5 GBq/μmole (500 mCi/μmole). In the static target we found that ammonia production reached equilibrium quickly, resulting in a production of 0.13 mmoles. The flow-through target generated 8 mmoles of ammonia for a 50 μA $\times$ 20 minute irradiation.

Conclusion

The flow-through target system for the production of ^{11}C-CH_4 provides increased radioactivity over single shot low volume, high pressure gas targets. The ^{11}C-CH_4 saturation yield is within experimental errors to that for ^{11}C-CO_2 under similar conditions and is 72% of calculated theoretical maximum yield, allowing for the support grid transmission. The cause for the relatively low specific activity is under investigation. The high quantity of ammonia co-produced will adversely affect the production of CH3I and must be removed for a useful system.

Experiment LS8
Radiotracers

(T.J. Ruth, TRIUMF)

(A.D.M. Glass, Botany Department, UBC)

During 2001–2002, my group has diminished in size as Ph.D. students completed their programs and two PDFs accepted positions as research associates elsewhere. Also, my long-time research associate, Dr. Yaeesh Siddiqi, retired. We have therefore made much less use of ^{13}N during this period. Nevertheless, in September, 2002, a visiting scientist joined my group and will possibly begin her Ph.D. studies in September, 2003, two new PDFs will begin their tenures in my laboratory in January, 2003, and a scientist from New Zealand will join my group in May, 2003. I therefore anticipate a renewed requirement for ^{13}N in the coming year.

Ph.D. students: Anshuman Kumar (current), Yu Wang (likely) Mamoru Okamoto, Dev Britto (completed). PDF: Manuela Simon, Yaeesh Siddiqi. Visitors: Herbert Kronzucker, Dev Britto, Yu Wang.

Rice research

Anshuman Kumar has now cloned three ammonium transporter genes from rice and successfully demonstrated that the expression of two of these genes (AMT1.1 and AMT1.2) is strongly correlated with root N status. By measuring ammonium influx using $^{13}NH_4^+$, he has shown that the control of influx, mediated via changes of root glutamine and asparagines, appears to be via changes of transcript abundance of AMT1.1 and AMT1.2. A third gene, AMT1.3, is relatively insensitive to root N status but is responsive to diurnal irradiance at leaf level. Thus a strong correlation was observed between the pattern of incoming light, AMT1.3 expression and ammonium influx.

Nitrogen uptake in trees

(Collaboration with CELLFOR: M.Y. Siddiqi, M. Simon, J.J. Vidmar)

Our goal of increasing nitrate uptake in plants overexpressing the high-affinity NO_3^- transporter gene, (AtNrt2.1) has been unsuccessful in tobacco and in poplar seedlings. Based on work on an algal model system, it appears that a second family of genes (the NAR2 family) must be co-expressed in order to achieve efficient NO_3^- uptake. Mamoru Okamoto (Ph.D. candidate) has cloned the algal counterpart from the higher plant Arabidopsis and we are investigating the importance of the Arabidopsis NAR2 homologue in mutants that are blocked in the expression of this gene. Preliminary findings suggest that the mutant is unable to grow normally when nitrate is the sole source of N. Assays of NO_3^- uptake will be conducted in standard fashion using $^{13}NO_3^-$.

$^{13}NO_3$ influx in the fungus aspergillus nidulans: a structure function study of gene sequence and NO_3^- uptake

(Collaboration with S. Unkles, J. Kinghorn, St. Andrews, Scotland; A.D.M. Glass, Y. Siddiqi)

Together with our Scottish collaborators, we have cloned and sequenced the two NO_3^- transporters of this

fungus. They have similar (but not identical) gene sequences but have very different affinities for NO_3^- and different maximum velocities.

Having the gene sequences and the physiological characterization, it will be possible to generate chimeric proteins and switch the gene's function from high to low affinity, etc. We will test the resultant strains using $^{13}NO_3^-$. This will make it possible to place NO_3^- transport kinetics on a sound structural basis and to manipulate transport within existing genes. This project has been on hold awaiting NSERC funding that is now in place. A PDF will begin this work in January, 2003.

Studies of fluxes and compartmentation of chloride ions in barley plants

(D.T. Britto, H.J. Kronzucker, Toronto)

With the increasing use of irrigation and fertilizers throughout the world, there have been associated increases in salt accumulation in agricultural soils, affecting ∼50% of the irrigated agricultural land base globally. Soil solution concentrations of sodium, chloride, and other ions can sometimes reach excessively high levels, resulting in suppression of plant growth and, ultimately, loss of arable land. Because of the severity of this problem, much research has been focused on salt stress and its avoidance by tolerant species or cultivars. However, while the physiology of plant-sodium relations has been particularly well studied, the chloride ion, which often accompanies sodium, has been understudied in relation to salt stress in plants. The objective of our study was to establish a baseline of information regarding the transport and subcellular accumulation of chloride in barley (Hordeum vulgare) roots, particularly with regard to the influence of nitrogen strength and source.

Due to the provision of short-lived radioisotopes of chlorine ($^{38,39}Cl$) provided by TRIUMF, we have made major progress towards this objective. We grew barley seedlings under ten nutritional conditions, varying both external chloride concentrations and nitrogen sources and concentrations. Chloride was varied between 0.1 mM and 100 mM externally, covering a range that included both benign and toxic concentrations. Nitrogen was provided as either ammonium (NH_4^+) or nitrate (NO_3^-), at low (0.1 mM) or high (10 mM) concentrations. We examined the influx, efflux, shoot translocation, subcellular turnover, and pool size of Cl^- under these nutritional conditions. We found that, overall, these parameters follow the general pattern we have observed using isotopes for other nutrient ions, particularly nitrogenous ones. Steady-state Cl^- influx increased with increasing external Cl^- and was generally lower when NO_3^- was the nitrogen source (in keeping with findings by other workers). Cl^- efflux increased to a greater extent along this gradient, resulting in a low efflux-to-influx ratio (10–20%) at moderate Cl^-_{ext}, and an exceptionally high one (∼90%) at high external Cl^-_{ext}. This ratio tended to be higher when NO_3^- was the N source. Because the efflux increased with Cl^-_{ext}, the resulting net flux (accumulation) increased much more moderately than either influx or efflux. The high fluxes observed at high Cl^-_{ext} suggested that there would be an associated high respiratory cost, as has been shown previously for NH_4^+, but preliminary respiration experiments have not demonstrated this.

Our results disagree with a previous model for cellular Cl^- compartmentation, which had maintained that this ion is held at a homeostatically constant concentration in the cytosolic compartment. What we observed using compartmental analysis by tracer efflux (CATE) was substantial variability in the size of this pool, and in its turnover, both of which increased with increasing Cl^-_{ext}. One question we wanted to pose was whether we would see high accumulation of Cl^- ions in the cytosol of plant cells exposed to high external NH_4^+, since we have found that high accumulation of the latter ion occurs cytosolically under this condition, and we hypothesized that Cl^- could act as a counterion to NH_4^+, providing electroneutrality to this metabolically critical cellular compartment. While we did observe a generally higher cytosolic accumulation of Cl^- with NH_4^+ treatments relative to NO_3^- treatments, this accumulation was not high enough to satisfy the anion requirement demanded by high cytosolic NH_4^+, and further possibilities must be sought.

Radiotracers for chlorine and sodium

Dr. Herbert Kronzucker of the University of Toronto (former student of Dr. Glass) is developing a program to study kinetics of various elements in plant systems. This past summer he returned to Vancouver to conduct a series of studies using $^{38,39}Cl$. These isotopes can be easily produced by irradiating natural Ar with protons of about 40 MeV as described in the literature.

^{110m}Ag in nuclear orientation experiments

(B. Turrell, Physics, UBC)

In April, 2001, the PET group made us a sample of ^{110m}Ag produced by proton irradiation of a Pd foil. This procedure also produces other silver isotopes, in particular ^{105}Ag. Measurements in our laboratory at UBC in May indicated that the activity of ^{110m}Ag was 280 μCi while that of ^{105}Ag was 3.5 mCi. However, the relative half-lives of two isotopes are 255 d and 40 d respectively. Therefore, by waiting a few months, the ^{105}Ag activity would decay by an amount sufficient that a low temperature nuclear orientation (LTNO) experiment on ^{110m}Ag could be performed.

The motivation for the experiment is that there have been relatively few studies of impurities in insulating, ordered magnets, and we decided to study oriented Ag nuclei in a suitable antiferromagnet to determine the hyperfine field which reflects the atomic magnetization. A previous experiment at Louvain-La-Neuve by a UBC-Leuven collaboration had indicated a small anisotropy for γ-rays in the decay of ^{104}Ag that had been implanted into $MnCl_2.4H_2O$. However, the sample temperature in this experiment was relatively high ($\sim$90 mK) and, subsequently, thorough analysis showed that this effect could not be distinguished from zero within experimental error. Therefore, the original intent of the present experiment was to dope ^{110m}Ag into the same crystal and perform an LTNO experiment at a much lower temperature ($\sim$35 mK).

In May and June, 2001, attempts were made to grow a crystal of $MnCl_2.4H_2O$ from a saturated solution of $MnCl_2$ containing both ^{54}Mn and ^{110m}Ag (and ^{105}Ag). The former grew into the crystal as expected, but very little of the silver isotopes went in. It was concluded that this was due to Ag being monovalent whereas Mn is divalent. A literature search was then made for insulating magnets with a composition that included a monovalent, metallic ion. The candidate that emerged was $Rb_2MnCl_4.2H_2O$.

This is an antiferromagnet with a Néel temperature TN = 2.2 K. We have grown some crystals of this salt, but we have to refine the technique to produce some plate-like samples, incorporating ^{54}Mn and ^{110m}Ag, on which to perform the LTNO measurements. We plan to do this in the next two or three months.

In the LTNO technique, one measures the directional distribution of radiation from an oriented ensemble of nuclei. For the axially symmetric case, the normalized intensity of γ-radiation in direction θ to the orientation axis, normalized to the warm count at 1 K, is given by

$$W(\theta) = \sum B_k A_k Q_k P_k(\cos\theta)\,. \qquad (1)$$

Here the B_k describe the orientation of the nuclei and contain the solid state information, the A_k depend on the observed and preceding transitions in the nuclear decay, the Q_k are detector solid angle corrections, and the P_k are the ordinary Legendre polynomials. Significant values of B_k are obtained when the nuclei experience a sizeable hyperfine interaction and are cooled to millikelvin temperatures in a dilution refrigerator.

In the decay of ^{110m}Ag, there are several γ-rays that can be studied, but an outstanding candidate for LTNO measurements is the 1384 keV transition. For this γ-ray the values of the A_k coefficients are A2 = 0.894 and A4 = 0.080. The hyperfine field, B_{hyp}, for the Ag nuclei is unknown. However, we note that Ag is a 4d element and, with one unpaired electron, we would expect $B_{hyp} \sim 35$ T. If we assume this value then, at temperature T = 40 mK, we would obtain for the B_k coefficients, B2 = 0.200 and B4 = 0.007. We can then estimate that the normalized intensities at $\theta = 0°$ and $\theta = 90°$, using $Q_k \approx 1$, would be $W(\theta) = 1.18$ and $W(\pi/2) = 0.91$. Measuring $W(\theta)$ in the experiment would allow B_{hyp} to be determined.

If a sizeable effect is indeed measured, we could then perform NMR on the oriented nuclei (NMRON). The NMRON technique not only measures the hyperfine field, B_{hf}, very precisely, but also the nuclear spin lattice relaxation (NSLR) and these give, respectively, details of the electronic magnetization and its dynamic behaviour. It is convenient for discussing NMRON to re-express Eq. (1) in the form

$$W(\theta) = \sum a_m(\theta) p_m\,. \qquad (2)$$

Here p_m is the population of a magnetic substate, labelled by m, and $a_m\theta$ includes the nuclear decay scheme and angular factors. NMR alters the substate population distribution and can be detected by observing the change in $W(\theta)$. The recovery to thermal equilibrium allows the determination of the NSLR time T1.

^{22}Na source for positron tomoraphy
(C. Thompson, McGill)

In positron emission tomography (PET), the most important correction required is the accurate measurement of γ-ray attenuation. Two approaches are currently used today: orbiting rod sources with 2D acquisition and single photon attenuation correction with ^{137}Cs. Rod-source windowing is the most widely implemented mechanism. ^{68}Ge/Ga rod sources rotate around the subject and, thanks to a coincidence circuit between two opposed detectors, the line of response (LOR) from the annihilation γ-rays is identified. The main advantage of this technique is the use of a concentrated source which reduces random events.

The collinearity criterion of both detectors and the orbiting rod sources eliminates most of the scatter events. Unfortunately the use of orbiting rod sources in transmission scans remains limited by low count rates due to close proximity of the near detectors.

The other alternative used is a rotating point source of 662 keV γ-rays of ^{137}Cs. This technique relies on the detection of photons in "single" mode rather than "coincidence" mode and no longer restricts the choice of transmission sources to those that decay by positron emission. The motivation for using ^{137}Cs as a transmission source comes from its higher count rate capability

due to a decreased detector dead time and increased object penetration. Since 662 keV γ-rays are being used for transmission, scanning measured attenuation coefficients will be 10% lower than 511 γ-rays of emission data and scaling of the measured attenuation factors to make them applicable to the emission data is thus necessitated. Several scaling methods are currently under study. Finally, a new approach using ^{137}Cs has been proposed by Jones *et al.* using collimated coincidence point sources with dedicated reference detector.

We propose a different approach of coincidence point sources using beta-gamma coincidence and 3D acquisition to improve the quality of transmission scans. This method would combine the advantages of single photon attenuation correction with ^{137}Cs without having the problem of scaling the attenuation coefficients due to a different energy from the annihilated photons. It is well known that a positron must lose an appreciable amount of its energy before annihilation with an electron can occur. In our case, the energy lost is spread inside a plastic scintillator material which produces light detectable by a photomultiplier tube (PMT). This PMT signal can then be used to trigger a coincidence circuit and identify a line of response between the plastic scintillator and the PET detectors. The concept of beta-gamma coincidence was proposed by our group in 1999 and used PIN diodes to detect the positron. This will be the first implementation of beta-gamma coincidence on an actual PET scanner.

^{38,39}Cl irradiations, targetry and chemistry

We converted the old neon target that was used to produce ^{18}F at 41 MeV (on the CP42) into a ^{38}Cl and ^{39}Cl-producing target ($t_{1/2}$ = 38–37.2 min; 39–55.7 min). At 41 MeV, the isotopic ratio for ^{38}Cl to ^{39}Cl is approximately 1.6. The experiment involved irradiating argon gas at a pressure equivalent to that of the Ne target (~300 psi) with a 41 MeV proton beam of 5–15 μA for times up to 30 minutes. The theoretical production rate is about 10 mCi/μA at saturation, thus we should be able to make <100 mCi. All the chlorine isotopes produced would stick to the walls of the aluminum target after they are produced. The gas can be vented directly since there are no gas phase radioisotopes produced with this method. The only other radioisotope (besides the chlorines) produced in any appreciable quantity is a small amount of ^{38}K (this would also stick to the walls of the target body) but since the half-life of this isotope is only ~7 min it can decay away almost entirely before delivery. The Cl ions are removed by rinsing the target with a rinse of water (~70 ml) which is returned remotely to the lab via argon pressure (10 psi). This procedure is conducted remotely. The chlorine is then trapped on a small ion exchange column, which can then be shipped to the Botany Department via the pipeline, or alternatively the chemist can elute the ions in a few ml of potassium carbonate that can then be shipped in a small vial.

Seventeen shipments were made during the 30 day period of July/August, 2002.

Production of ^{110m}Ag

A stack of two natPd foils was bombarded in February, 2000. The chemical processing involved dissolving the palladium target, removing excess acid through evaporation followed by taking up the Pd in 0.01 M HCl. The Pd and Ag are separated on an alumina column with the Pd fraction eluting with the 0.01 M HCl. All indications are that the Ag fraction remains at the top of the column. Once all of the Pd has been removed as evident by colour change of the column, the Ag fraction can be eluted with 0.1 M HCl. The Ag is eluted in less than 10 ml.

Aliquots of both fractions were assayed for radioactive species. The Pd fraction does not have a strong γ-ray for identification. We will have to develop a technique to determine the relative radiochemical purity although from the colour change on the column we are certain that it is greater than 90% separation.

The silver fraction contained radioisotopes which could be identified as $^{105,\,106m,\,110m}$Ag. We performed a γ-ray spectroscopic analysis on the unseparated foil to estimate production rates. The estimated EOB yields are as follows:

^{105}Ag-combined foils – 26 mCi/μA at saturation;

^{106m}Ag-combined foils – 2.3 mCi/μA at saturation;

^{110m}Ag-combined foils – 0.75 mCi/μA at saturation.

At this rate it would require about 1250 μA h to achieve the required 100 μCi. However the coproduction of ^{105,106m}Ag would be about 15 and 2.2 mCi, respectively. The exact mix would depend upon the beam current and length of bombardment.

In order to proceed we have had to modify a target so that we can irradiate with a beam of about 50 μA. At this intensity it will require about 25 hours of beam that could be spread over several days. Following irradiation, the foil would be left in place for at least 40 days to allow the decay of ^{105}Ag (50% remaining) and ^{106m}Ag (0.04 remaining).

In January, 2001 a Pd foil was irradiated at approximately 35 μA for a total proton dose of 90011 μA min (1500 μA h). We allowed the various radioisotopes to decay for 3 months before performing the chemical separation. In early May the dominant radioactive species were ^{105}Ag 3.5 mCi and ^{110m}Ag 280 μCi.

An additional Pd foil was irradiated in August, 2002. Processing will be performed in January, 2003.

Implantation of ^{22}Na

Two 10 μCi sources will be prepared by implanting the separated ^{22}Na into plastic scintillator material. At a rate of 10^9 atoms/s it would take about 12 hours of beam time per source. A beam flux of 10^{10} atoms/s (which has been achieved at ISAC) would obviously enable the experiment to be performed in less than 2 hours for each source. To control spot size, a mask will have to be used which will lower the effective implantation rate.

Experiment LS29
Production and distribution of FDG for clinical studies

(T.J. Ruth, TRIUMF)

Final report

Following the workshop on the distribution of FDG held at the LSPEC Review of 1996/1997, discussions ensued as to how best to provide FDG to the local community for clinical utility. There is no mechanism established for the real-cost reimbursement. In addition, TRIUMF management does not wish to engage in a commercial venture dealing with radioactive substances. However, there continues to be interest in access to FDG and other tracers, both for research purposes and for clinical applications. While the research uses for these tracers can continue to be supplied under existing protocols, there is still a growing need for access to large quantities of either the radiopharmaceuticals such as FDG or ^{18}F-fluoride as precursor.

Since this project's first submission in 1998 a number of new and continuing developments warrant mentioning. First, a local company, IPET, has established a pay-for-fee Clinical PET Centre at the BC Research Facility adjacent to TRIUMF. IPET tried negotiating with MDS-Nordion for the supply of FDG. As indicated above, TRIUMF has chosen not to be involved as a supplier for non research purposes.

Over the last year IPET has received an Investigative New Drug application from Health Canada for the safety of ^{18}F-FDG prepared on the IPET site. That trial was completed in December, 2001. IPET has begun a Clinical Trial Application for the efficacy of FDG in monitoring metabolic status in cancer patients. In addition, MDS Nordion has expressed interest in supplying ^{18}F-fluoride once their new TR30 cyclotron has been installed and commissioned.

The Vancouver General Hospital is currently modifying its manufacturing laboratory to allow the production of ^{18}F-FDG. This site will receive the ^{18}F-fluoride from TRIUMF and, using the method of Hamacher *et al.* will synthesize the ^{18}F-FDG. After quality control, this material will be sent to all hospitals that have research proposals for clinical use of ^{18}F-FDG. The proposal is for TRIUMF to ship ^{18}F-fluoride to VGH twice a week (1 Ci per shipment). The object of this project is to gain experience in routine clinical supply of ^{18}F-FDG. From this experience we will prepare and submit a CTA and eventually a new drug application (NDA) which will allow the routine distribution of ^{18}F-FDG in British Columbia.

It should be noted that MDS Nordion has been approached to supply ^{18}F-FDG alone or ^{18}F-fluoride to VGH in a similar arrangement and they have refused.

With the transfer of the production of FDG from TRIUMF to VGH, this LSPEC project comes to an end and a separate mechanism needs to be considered.

BC Children's Hospital: No progress has been made on this project in 2002.

Vancouver General Hospital (Oak Street Site): A total of 24 FDG shipments were made in 1999, a further 30 shipments in 2000, 24 in 2001 and 18 in 2002, all part of LS28 and LS47.

St. Paul's Hospital: A total of 19 shipments of FDG were made in 2002 as part of LS48, 49 and 54.

Lions Gate Hospital: A total of 15 FDG shipments were made in 1999 and a further 27 shipments in 2000, 35 in 2001 and 42 in 2002 (see LS24 and LS41.

Over the last 4 years, TRIUMF has supplied 232 batches of ^{18}F-FDG to the local hospitals as well as 30 batches of ^{18}F-tracer for physics experiments. This program has been a success enabling the local clinicians to develop realistic protocols for using positron tracers for diagnosis in their patient populations. Now that the use of FDG has reached a clinical stage the support from LSPEC should be terminated and a new direction should be explored whereby TRIUMF/MDS Nordion can consider supplying the radiochemical ^{18}F-fluoride, with the production of FDG being handled by the lab in VGH.

No reports for the more clinically based projects will be presented (LS24, 28, 41, 42, 47, LS48, 49 and 54).

LS29 has evolved into LS58, production and distribution of FDG for clinical studies.

Experiment LS32
^{18}F-$H_2{}^{18}$O supply to the University of Alberta

(T.J. Ruth, TRIUMF)

Final report

Purpose: This project provided the researchers at the University of Alberta with ^{18}F-fluoride to support the development and commissioning of a new PET facility located in the Centre of Biological Imaging and Adaptive Radiotherapy (CBIAR) at the Cross Cancer Institute.

The research involved three primary aspects: i) a training component, ii) a radiopharmaceutical devel-

opment component, and iii) a technology assessment program for translational research.

i) Two staff from the University of Alberta spent a combined period of 9 months learning to operate and perform routine maintenance for the TR13 cyclotron in preparation for the delivery of their machine in Edmonton.

The staff at the University of Alberta PET Centre used the ^{18}F to gain experience in the labeling and handling of fluorinated compounds having applications in oncology. Proficiency in the operation and modification of the automated synthesis of commercial radiopharmaceutical modules supplied by Coincidence Technologies and Ebco Technologies was gained by both students and staff at CBIAR-PET. In particular, skills have been acquired for the preparation and use of ^{18}F-fluorodeoxyglucose (FDG). The vaule of FDG in cancer diagnosis and in the assessment of treatment outcomes has been well documented.

ii) A second project has established a synthesis of ^{18}F-estradiol using a semi-automated synthesis apparatus. The product will be used in a research project to identify and determine treatment outcomes of breast cancer patients who show positive estrogen receptor status in their disease. The PET Centre has received funding from the Canadian Breast Cancer Foundation, which has assisted in the development of a semi-automated synthesis unit for the ^{18}F-estradiol. The development and preliminary investigations with these agents required routine supply of ^{18}F-fluoride. This material has not yet been used in human studies.

iii) A descriptive and analytical epidemiology study of primary lung cancer in a 1998 Alberta cohort was completed and submitted for publication. The cohort's health care utilization experience, both in terms of costs and volumes of specific interventions, was analyzed using regression analysis to derive a cost formula. This phase is nearing completion. The final phase is to model our data (FDG PET in lung cancer), with respect to the costs benefit and survival. Modelling will initially use the methodology published by Gambhir and co-workers.

The cost effectiveness of FDG PET for other cancers was also explored in a manner similar to that described above. We are still in the introductory information gathering stage.

The activity received allowed for a total of 655 ^{18}F-FDG PET scans (ADAC C-PET) of which 598 were new patients and 67 were follow up PET scans for further assessment.

Summary

The delivery of ^{18}F from TRIUMF was established in the first quarter of 2001. The shipping schedule provided the delivery of one shipment per week, transported by ground carrier to Vancouver International Airport and then as Air Canada Dangerous Goods to Edmonton. Originally the irradiations were performed by the TRIUMF PET Chemistry group but at a later stage a chemist from Edmonton trained to perform the operations from the period December, 2001 to September, 2002.

- Produced a total of 178 Ci of ^{18}F from the TR13 cyclotron of the PET group at TRIUMF for shipments to Edmonton.
- Edmonton received a total of 16.8 Ci in 125 shipments (12 January to 19 September, 2002).
- The Edmonton cyclotron began producing ^{18}F on 19 September, 2002.
- MDS Nordion provided the packaging and shipping in Vancouver.

Experiment LS33
Evaluation and improvement of a dual head coincidence camera
(V. Sossi, UBC)

The performance measurements of the Siemens E.Cam Duet camera located at St. Paul's Hospital have been completed and submitted for publication.

Quantification studies for dual head coincidence imaging

The development of the analytical scatter correction is progressing. Since the last report, significant development of the scatter correction calculation for single scatters has been achieved. The sofware is written in Matlab because of its flexibility, portability and simple memory management. Some preliminary scatter distributions have been obtained for simple cylindrical phantoms. These results are being compared to results from Monte Carlo and initial results show the correct gross features of the scatter distribution.

The COincidence Data Examiner (CODEX) graphical user interface software for analyzing simulated data sets from SimSET is under continual updating, debugging and feature adding. CODEX is being updated to also analyze ADAC MCD dual head camera measured data and output from the scatter and randoms calculation code.

Presently the MCD camera does not have a correction for random events. A new method for random correction is therefore under development.

Matlab code to perform Fourier rebinning (FORE) [Defrise *et al.*, IEEE Trans. Med. Imaging **16**, 145 (1997)] is still in the process of development and needs to be completed. This is necessary to handle the scatter and randoms from oblique angles in the scatter and randoms correction code. This will be used to study

the effects of FORE on image quality and will be compared to measurements done on the MCD camera using FORE. The spatial resolution of the MCD camera will be measured and the data will be used to validate the FORE code.

Research plan

The scatter correction development

The optimization of the scatter correction code is continuously ongoing. The following issues are being investigated:

- Effects of detector materials and axial shielding, are still being studied to improve the accuracy of the calculation.
- The choice of scatter calculation parameters, such as object and angular sampling.
- The possibility of pre-calculations of a "scatter system matrix" which would only require the manipulation of the specific emission and transmission data for the scatter calculation. This is needed to speed up the calculation.
- A graphical user interface to simplify the set-up and use of the scatter correction and to interface with the CODEX environment.

When correct results are obtained for simple cylinders then scatter distributions in anthropomorphic phantoms (Zubal phantom) will be studied in comparison to results from Monte Carlo simulations. As well, when the correction code is fully validated with simulation studies a number of phantom studies will be done on the MCD camera.

Random correction method development

A new random correction method is under development.

Experiment LS35
Development of ^{18}F labelled nitroimidazole PET imaging agents for tissue hypoxia

(M.J. Adam, TRIUMF)

Hypoxia in cells and tissues is an important component of various pathological states (e.g. ischemia and stroke). Hypoxic tumour cells are extremely important within cancer treatment because they are more likely to survive radiation and chemotherapy, leading to an increase in tumor resistance to treatment. More recent evidence suggests that hypoxia is related to the aggressiveness of disease. Such studies employed a microelectrode, used in many centres, but were limited because of invasiveness and requirement for an accessible tumour.

Derivatives of 2-nitroimidazole are used extensively as hypoxia markers. The 2-nitroimidazoles are not metabolized in oxygenated tissues, but bind to macromolecular proteins after reduction in hypoxic cells. This permits detection by a variety of techniques. For example, the products of such binding for the (pentafluoropropyl)acetamide (EF5) and (trifluoropropyl)acetamide (EF3) derivatives of 2-nitroimidazole can be detected by specific fluorescent antibodies.

The synthesis of ^{18}F-EF5 has now been developed and was achieved by preparing the allyl percursor and fluorinating it with ^{18}F elemental fluorine in trifluoroacetic acid. The radiochemical yield is 17% after HPLC purification.

Several syntheses have been performed for cell and animal studies. Initially we carried out cell studies to determine the effects of hypoxic and aerobic conditions on the uptake of EF5. This experiment indicates that about 10-fold more hot EF5 is concentrated in cells under hypoxic conditions as compared to aerobic conditions, and that the addition of cold EF5 has little effect. The gamma counting results were basically the same as those obtained by using cold EF5 and flow cytometry. These cell experiments were followed by rat experiments; rats with 9L tumours were injected with ^{18}F-EF5 and imaged on our PET tomograph, followed by dissection to determine biodistribution. An image of the brain tumour in the rat was obtained. The next stage of the research is to proceed to human studies.

Progress this year has been slow due to a lack of funds and the fact that a researcher at the Cancer Research Center (BCCRC) has not taken this project on as a priority. However, this has now changed and Dr. Donald Yapp has been hired by BCCRC to champion this project. A British Columbia Lung grant to Skov and Gelman will allow for an initial screening test of cold EF5 in 12 patients along with 6 hot EF5 experiments in humans. Ethics approval for these experiments is still required. Since Dr. Yapp's involvment, several other researchers have become more interested in using EF5 in their research. We expect to be able to carry out human imaging early in 2003.

Experiment LS39
Positron emission profiling (PEP) for pulp and paper fluid dynamic studies

(T.J. Ruth, TRIUMF)

Recently positron emission profiling has been shown to have utility in following certain physiochemical processes that have aided in the understanding of the mechanisms of these processes. The models used to describe the motion of fibres in the manufacturing of paper are limited by a lack of understanding about the micro-dynamics of the interaction of the various fibre sizes during motion. By labelling the fibres with a positron-emitting isotope, it may be possible to monitor the sedimentation process to provide better parameters for the models.

Previously we have visualized the motion of different fibre sizes during sedimentation and we are in the midst of developing this method to visualize fibre motion in a new geometry, namely a hydrocyclone. A hydrocyclone is an industrial apparatus used to separate fibres into different length or weight fractions.

Flow visualization of a hydrocylone using PET with applications for the pulp and paper industry

Papermaking fibres are hollow, flexible rod-like particles that have a wide distribution in both length and diameter depending upon species and growing conditions; when liberated from the tree they can curl or kink. North American fibres are typically 40–50% cellulose, 20–35% hemicellulose, 15–35% lignin, with the remaining fraction containing resins, tannins, ash and miscellaneous compounds. Solid-solid separation of papermaking fibre suspensions is of importance to the pulp and paper industry. Traditional unit operations such as screening, cleaning, and fractionation are traditionally described as solid-solid separation processes. For example, during fractionation, a dilute fibre suspension is separated into a number of different length-fractions. Despite the longstanding use of these unit operations, little is known about the mobility of the various fibre fractions that make up the suspension. One of the essential difficulties lies in the incomplete understanding of the long-range multi-body hydrodynamic interactions. Another difficulty is that these properties are strongly dependent upon the microstructure of the suspension which itself changes as these fibres tend to mechanically entangle or flocculate. Ascertaining these effects is not easy as these suspensions are opaque and difficult to visualize at reasonable penetration depths. These issues make the understanding of the behaviour of these suspensions particularly difficult. Clearly, there is a need to visualize the motion of the individual classes of components in a fibre suspension in order to better control the physical properties of paper.

Over the last number of years, we have conducted gravity-settling experiments at TRIUMF to test the feasibility of using PET as the visualization method. In this work, a selected class of fibres was radioactively labelled and allowed to settle in an untreated fibre suspension. The suspension was agitated and allowed to settle under the action of gravity in a cylindrical jar. Last year a similar study was carried out and we have now used these data to develop a mathematical description of the motion of fibres in a network. From these studies it is clear that this visualization technique has the potential to help clarify the behaviour of mixtures of fibres. We would like to extend this technique to measure the motion of fibres in a flowing device, in general, and to a hydrocyclone, in particular. We propose a hydrocyclone as this device (i) has relevance to industry; (ii) has a size and is operated in a manner which allows for PET profiling; (iii) has a geometry that is amenable to numerical analysis; and (iv) is supported by local experts in Vancouver who would help develop an industrially-relevant experimental protocol.

Recently, we have tested the feasibility of this idea by building a "transportable hydrocyclone" which we could profile using PET. An initial test of this configuration was conducted on November 18.

Experiment LS42
Configuration modelling and image reconstruction studies on a depth encoding research tomograph
(V. Sossi, UBC)

This study can be logically divided into two parts: simulation of the effect of the γ depth of interaction correction on resolution uniformity, and development of an optimum reconstruction algorithm for a depth encoding, list mode acquisition, high resolution research tomograph (HRRT). The first part has been completed and submitted for publication while studies relative to the second part are still under way.

Simulation of the effect of the γ depth of interaction correction on resolution uniformity

One of the most important parameters in positron emission tomography (PET) imaging is detection sensitivity, since it has a direct bearing on the statistical quality of the images. Detection sensitivity is proportional to the tomograph solid angle and a cost-effective way of increasing the solid angle is achieved by reducing the detector-to-detector distance. However, such reduction increases the fraction of detected events where the γ-ray hits the detector surface at an oblique angle, thus reducing the probability of the interaction to occur in the same crystal, where the photon first entered the detector. This leads to the parallax error, which can significantly degrade the position resolution uniformity. The parallax error can be reduced by determining and accounting for the depth of the γ interaction (DOI) in the crystal. Several DOI determination schemes have been proposed [Jones *et al.*, "LSO PET/SPECT Spatial Resolution: Critical On-line DOI Rebinning Methods and Results", CTI PET Systems Inc., Free University Hospital (Amsterdam, Netherlands); Moses *et al.*, J. Nucl. Med. **32**, 995 (1991); Moisan *et al.*, IEEE Trans. Nucl. Sci. **42**, no. 4 (1995)] and one of them is currently implemented in a human size brain tomograph, the high resolution research tomograph (HRRT) [Wienhard *et al.*, IEEE Trans. Nucl. Sci. **49**, no. 1 (2002)]. This scheme employs a two-layer crystal configuration, where the two crystal layers are characterized by two different scintil-

lation decay times. Pulse shape discrimination is used to distinguish events originating from each layer [Wienhard *et al., op. cit.*]. We have evaluated the impact of such a correction scheme on the resolution uniformity for the HRRT geometry (octagonal design) using GEANT and a modified version of DETECT and compared it to that obtained for a circular tomograph design with the same detector-to-detector distance. In both cases four crystal configurations were simulated: two LSO layers 7.5 mm deep (LL_7.5), two LSO layers 10 mm deep (LL_10), a 7.5 mm deep LSO layer followed by a 7.5 mm GSO (LG_7.5) layer and finally a 10 mm deep LSO layer followed by a 10 mm deep GSO layer (LG_10). Resolution with and without DOI correction is presented in Table XIII. It can be observed that both the absolute resolution and resolution uniformity improve significantly with DOI correction for both tomograph configurations [Astakhov *et al.* (submitted to IEEE Trans. Med. Imag.)].

Table XIII. Overall spatial resolution for three source positions. Data are shown in the format a/b, where a is the resolution obtained with DOI correction and b is the resolution obtained without DOI correction. All values are expressed in mm.

	Crystal config.	0 cm	5 cm	10 cm
Octagonal geometry	LL_7.5	1.9/2.0	1.9/2.2	2.1/2.9
	LL_10	2.0/2.6	2.0/2.7	2.3/3.6
	LG_7.5	2.1/2.4	2.1/2.5	2.5/3.4
	LG_10	2.3/3.0	2.4/3.1	2.8/4.1
Circular geometry	LL_7.5	1.4/1.4	1.9/2.2	2.0/2.9
	LL_10	1.4/1.4	2.0/2.6	2.1/3.3
	LG_7.5	1.6/1.6	2.2/2.5	2.3/3.3
	LG_10	1.6/1.6	2.3/3.0	2.3/3.7

Image reconstruction strategies for the HRRT

The HRRT, when used in fully 3D mode, provides a total number of 4.486 billion LORs. In a dynamic scanning situation the duration of a time frame is often so short (30 s or less) that the number of acquired events might be much less than the number of bins in a full sinogram data set. A reconstruction algorithm that would not require event histogramming might thus reduce the size of the data sets. An additional advantage of list mode acquisition is the elimination of the need to *a priori* define frame duration.

We have thus developed and implemented an attenuation-normalization weighted listmode expectation maximization (EM) algorithm (ANW-LM-EM), based on the approach originally developed by A. Reader *et al.* [Phys. Med. Biol. **43**, 835 (1998); *ibid.*, IEEE Nucl. Sci. Symp. Conf. Record. **3**, 1853 (2001)]. In this algorithm the image update is based on the following expression:

$$\lambda_j^{m+1} = \frac{\lambda_j^m}{\sum_{i=1}^{I} p_{ij}} \sum_{k=1}^{N} p_{i_k j} \frac{1}{\sum_{j=1}^{J} p_{i_k j} \lambda_j^m}$$

where λ_j^m is the m^{th} iteration of the image estimate for pixel j, k is the event and i is the LOR index. Preliminary results obtained with this algorithm are shown in Fig. 159. Currently we are exploring various random event correction schemes and evaluating the quantification accuracy of various statistical reconstruction algorithms.

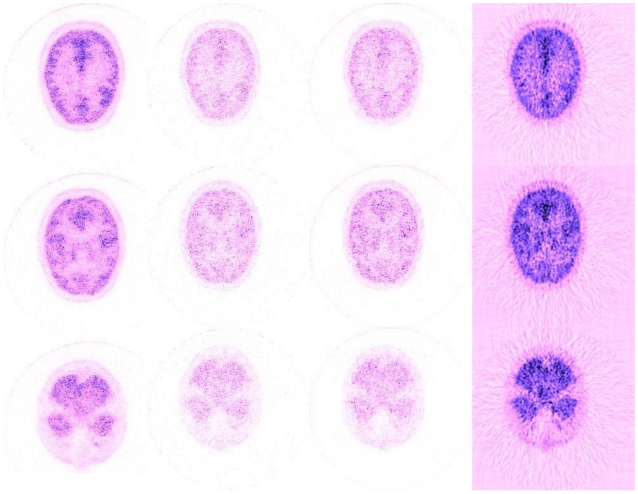

Fig. 159. Three different slices through images reconstructed using different reconstruction schemes. Columns, from left to right, correspond to LM-EM (1B counts), LM-EM (0.5B), 3D-OSEM (0.5 B) and FORE+2D-FBP (0.5 B).

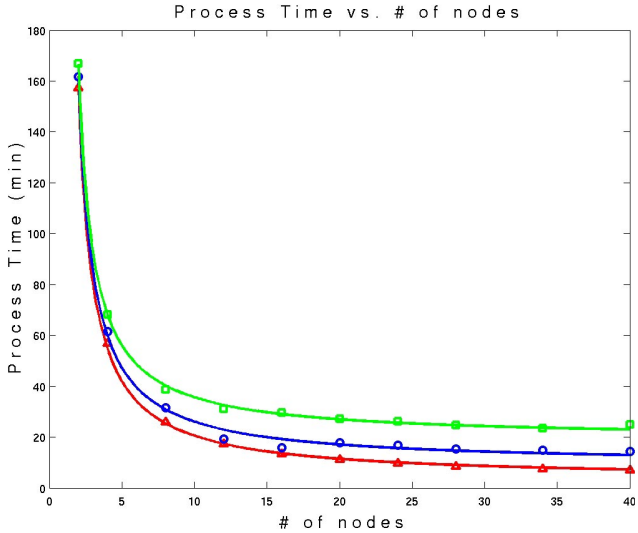

Fig. 160. Processing time for iterative list mode reconstruction for 40 M events as a function of number of 1 GHz Pentium nodes. Lower curve: 8 subsets ($x = 0.98$), middle curve: 32 subsets ($x = 0.94$) and upper curve: 64 subsets ($x = 0.88$) where x is the parallelized fraction of the reconstruction code.

We are also in the process of exploring various parallelization methods for the statistical reconstruction methods using a Linux cluster (Fig. 160).

Printed paper sources

Since the resolution of current scanners approaches 1–2 mm, it is important that the size of the sources used to measure the resolution is very small. We have successfully tested a set of printed sources using a regular ink-jet printer. We are currently refining the printing procedure and exploring possible source holder mechanisms.

Future work

The following topics are either on-going or to be started:

- Data reconstruction techniques with particular emphasis on random correction.
- Final design of a point source to map the tomograph point spread function.
- Implementation of the ^{22}Na source mechanism developed by Prof. Chris Thompson to investigate the impact of his time alignment procedure on this scanner.
- Detector normalization algorithms.
- Data transfer and storage schemes.
- Patient motion correction.

Experiment LS50
Antisense imaging nucleic acids for Parkinson's disease
(H. Dougan, TRIUMF)

For many years, Parkinson's disease has been a principal research interest of the TRIUMF PET group and the Neurodegenerative Disorders Centre at UBC. Many imaging agents labelled with positron emitters have been developed at TRIUMF for this program. Recently the UBC collaborators introduced Parkinson's related antisense DNA directed to the D2 receptor mRNA and to dopamine transporter mRNA into rat brains. The rats developed behavioural disorders and biochemical changes consistent with depletion of the "sense" mRNA by the "antisense" DNA probe. Last year's Annual Report related how the UBC investigators wished to extend their observations with unlabelled DNA to make new imaging agents based on DNA radiotracers. Progress was made at TRIUMF during 2002 developing radioactive ligand, (4-halogenbenzyl)-2-bromoacetamide (BBA) capable of labelling the needed antisense DNA. The chemical reactions leading to radiofluorine [^{18}F]F-BBA and the labelled DNA were carried out and examined in detail. It was determined that the reactions were too difficult and inefficient to be practical for the routine preparation of ^{18}F DNA in the immediate future. This prompted the radiofluorine chemists to commence development of innovative practical methods for obtaining ^{18}F DNA. Meanwhile it was decided to work with the more attainable radioiodinated I-BBA and DNA modified with I-BBA ligand. Antisense DNA was first made modified with the non-radioactive I-BBA ligand and tested for biological activity in rat brains. Rats developed the characteristic behavioural disorders in the presence of antisense DNA modified with I-BBA. Finding reduced D2 receptor levels will be a further test of whether I-BBA interferes with antisense DNA activity. A mass spectroscopy technique was developed with the UBC Mass Spectroscopy Unit, which verified that the DNA bioconjugates had the expected mass. Radiolabelling antisense DNA proceeded successfully with [^{125}I]I-BBA, leading to [^{125}I]DNA at nearly 2,200 Ci/mmole. We hope to utilize the [^{125}I]DNA to visualize the site of antisense action in the rat brain by autoradiography.

Experiment LS51
Auger therapy for prostate cancer
(H. Dougan, TRIUMF)

Radioisotope induced therapy is of interest at TRIUMF because numerous radioisotopes possessing diverse decay characteristics are available here. Project LS51 examines the treatment of prostate cancer through DNA damage and cell killing induced by the Auger electrons released following the decay of ^{123}I and ^{125}I. Radioiodine incorporated into an iodoandrogen steroid is brought into proximity of DNA by the androgen receptor protein (AR); the cancer cell DNA is consequently targeted by the Auger electrons of the radioiodine decay, followed by death of the cancer cell. Prostate cancer is the most prevalent cancer in men and the second leading cause of cancer death in Canada. The Auger therapy research is carried out in collaboration with the Prostate Centre in Vancouver. Additional explanation of the prostate cancer biology was given in last year's Annual Report. In progress to date, stannyl precursors have been prepared for two suitable iodoandrogen steroids (EMIVNT and ZMIVNT) with potential for Auger therapy. The stannyl precursor permits [^{125}I]EMIVNT to be prepared with approximately 2,200 Ci/mmole, while [^{123}I]EMIVNT is labelled to much higher specific radioactivity. The binding of [^{125}I]EMIVNT has been assayed with androgen receptor (AR) from the rat and human. It was found that EMIVNT binds AR with roughly the affinity of the natural ligand, testosterone, so that EMIVNT will be useful for tests of Auger therapy. The potential of EMIVNT for AR-dependent Auger electron cell killing will presently be determined in cancer cell strains at the Prostate Cen-

tre. Two of the strains express AR while two strains do not express AR. The team at The Prostate Centre is prepared to characterize the biochemical changes induced by Auger decay, and to attempt Auger therapy in whole animals.

Experiment LS52
Comparison of commercial FDG synthesis systems

(T.J. Ruth, TRIUMF)

Final report

Scientific justification

The production of ^{18}F-FDG involves the production of ^{18}F-fluoride, typically in a target chamber containing ^{18}O-H_2O followed by reaction with mannose triflate and subsequent de-blocking of the protected sugar resulting in the production of the ^{18}F-fluorodeoxyglucose. These steps are generally controlled by one of several commercially available synthesis systems. The efficiency for the conversion of the label varies between 50 and 70%. The cause of this variability is not understood.

This retrospective study was aimed at determining the efficiency of ^{18}F-FDG production from several commercially available automated synthesis systems. In addition, a comparison of the efficiency for the incorporation of ^{18}F-fluoride was made as a function of the target chamber used to produce the ^{18}F. In addition, the yields from the various boxes were compared.

Description of the research

All synthesis systems made use of the Hamacher method where fluoride displaces the triflate-leaving group and the labelled acetylated fluorodeoxyglucose is then de-blocked using either HCl or NaOH. The yields were determined by comparing the quantity of ^{18}F-fluoride at the start of synthesis and the quantity of FDG produced at the end of synthesis. Values were decay corrected to a common time. In addition, the quality control metrics of the final product were compared for each unit. For the production of ^{18}F-fluoride, the $^{18}O(p,n)^{18}F$ reaction was used with a $H_2{}^{18}O$ target on either a 13 MeV cyclotron (TR13) with a niobium target chamber or an 11 MeV cyclotron (RDS111) using a silver target chamber. For the production runs at the PETScan facility the ^{18}F-fluoride was loaded onto an ion-retardation resin before shipment from either P.E.T. Net in Seattle (about 3 hours for transit) or the TRIUMF facility (about 30 minutes). The shipments to Edmonton (about 8 hours) and Vancouver General Hospital (about 2 hours) involved shipping the irradiated water.

The three commercial synthesis units (Coincidence at the Cross Cancer Centre, CTI-CPCU at the PETScan Centre and the Ebco unit at VGH) provided similar yields (approximately 60% decay corrected) while the two targets had a significant difference in the yield of FDG, 60% for the niobium target body vs. 50% for the silver target body. All units provided FDG of the highest quality, meeting USP specifications.

The results of this study were presented at the Canadian Society of Nuclear Medicine Annual Meeting in Edmonton in April.

From these results it appears that the commercially available synthesis units provide similar yields of FDG with comparable quality of final product. While the results from VGH appear a little lower than the other two sites, the number of runs is small and the uncertainties associated with these results certainly overlap with those of the other units.

However, the efficiency of FDG production appears to be dependent upon the source of ^{18}F-fluoride. The yields using the same synthesis system (at PETScan) gave statistically significant different results for the two sources of ^{18}F-fluoride. The ^{18}F-fluoride produced in the niobium target body provides higher yields than a silver target body. The reason(s) for this difference is not understood and is currently under investigation to determine whether the material for the target chamber is the primary cause or whether radiolysis to the resin during shipment causes a poorer reactivity of the ^{18}F-fluoride ion. Another possibility is the purity of the target material ($H_2{}^{18}O$) for producing the ^{18}F. It should be noted that P.E.T.Net claims to have >65% FDG yield for in-house productions which could eliminate the target and water as problems.

Experiment LS53
Synthesis of ^{99m}Tc and ^{186,188}Re sugar derivatives

(M.J. Adam, TRIUMF)

An NSERC strategic grant was awarded (October, 2001, M.J. Adam, PI, $78,200/year for 3 years) to carry out research on the synthesis of technetium and rhenium labelled carbohydrates for use in nuclear medicine imaging and therapy. Dr. Adam is collaborating with Dr. Orvig in the UBC Chemistry Dept. and AnorMED (M. Abrams, CEO). A post doctoral fellow (Dr. Simon Bayly) and a graduate student (Cara Fisher) have also been working on this project for approximately one year.

Radiolabelled carbohydrates have been of significant interest to nuclear medicine due to the success of 2-^{18}F-fluoro-2-deoxy-glucose (FDG) as an imaging agent in positron emission tomography (PET). This success has naturally raised the question of whether a single-photon emitting glucose analogue with similar properties to FDG can be developed for use with single-

photon emission computed tomography (SPECT). Because of the relatively short half life of ^{18}F (110 min) its use is limited to facilities that have an accelerator in close proximity to chemistry laboratories and medical facilities. This fact makes it impractical for the FDG method to be widely used in medicine. ^{99m}Tc is the most widely used isotope in SPECT due to the fact that it is a generator produced, commercial isotope which makes it convenient to use and relatively inexpensive. It also has ideal physical properties for imaging. The drawback to this isotope is that it must be attached to the molecule via a chelate or organometal conjugate, which may perturb the system being studied. A SPECT analogue based on a widely available isotope such as ^{99m}Tc would make these agents available to the broader medical community. Among elements of the same series as Tc, the isotopes ^{186}Re and ^{188}Re show promise in the development of therapeutic strategies. For a β-emitting radioelement to be therapeutically useful, a half-life of between 12 h and 5 days is preferred: moreover, for a 1 MeV β-particle, the depth of penetration into tissue is approximately 5 mm. Furthermore, if some of the disintegrations are accompanied by 100–300 keV gamma photon, the behaviour of the radioelement can be conveniently followed by using a gamma camera. The nuclear properties of ^{186}Re and ^{188}Re are optimal for these purposes.

There has been significant progress in the first year with both the organometallic approach and the chelation approach. Cara Fisher has synthesized several ferrocenyl sugars including some that have not been reported before. Attempts to carry out the DLT reaction on these have proven difficult and new routes to the Cp-tricarbonyl metal compounds are being planned. Simon Bayly has established the aqueous based rhenium chemistry in the lab and has prepared at least one sugar-Re complex. The next step will be to prepare a chelate of the ^{99m}Tc radioisotope. A conference presentation and a paper are being prepared for submission in 2003.

Experiment LS57
Quantitative imaging with the Concorde microPET
(V. Sossi, UBC)

The UBC/TRIUMF PET group has recently been awarded funds to purchase a small animal scanner (CFI, BCKDF – P.I. Dr. T. Ruth). The Concorde microPET R4 (rat scanner) has been identified as the scanner of choice. Scanner delivery is expected in April, 2003.

Although the tomograph is a commercial scanner, the quantitative aspect of the data has not been fully characterized and implemented. We are proposing to assess the quantification accuracy of the camera and to implement an iterative list mode reconstruction code. We are also planning to improve the quantification algorithms, if they are found not to be sufficiently accurate. In addition we want to implement the time alignment method developed by Prof. C. Thompson on this camera and compare its impact on the camera performance to that observed on the HRRT. The currently proposed studies are:

- Performance of phantom studies to assess the quantitative accuracy of the camera.
- Implementation of a list mode reconstruction algorithm for this camera based on the work performed for the HRRT (see LS42).
- Design of a point source to map the tomograph point spread function based on the paper point source design (see LS42).
- Implementation of the ^{22}Na source mechanism developed by Prof. Thompson to investigate the impact of his time alignment procedure on this scanner.

Since the data acquisition hardware and software of the microPET R4 and the HRRT have many similar aspects (LSO crystals, list mode acquisition capabilities), many of the studies proposed here are a natural extension of the work being developed for the HRRT (LS42). We are therefore in a unique situation where we can directly transport the expertise acquired in a human sized tomograph to a small animal imaging situation.

We are concentrating on the data quantification and image reconstruction aspect of small animal imaging, since they are a prerequisite condition to obtaining biologically meaningful information. Once this part is completed we anticipate the development of new imaging protocols associated with small animal scanning, in particular the development of bloodless scanning protocols. This will be an exciting area of investigation and we anticipate it to be a natural continuation of the studies proposed.

It is also important to provide a short overview of the breadth of the medical and biological research to be performed with the R4, since it will expand the current PET applications at UBC/TRIUMF and will require the development of new imaging agents and protocols. The proposed research to be conducted with the R4 spans the neurosciences, physiology, enzyme chemistry and tumour biology. In the neurosciences the microPET will complement and extend numerous studies already under way in the human UBC/TRIUMF PET program such as dopamine turnover, antisense studies and gene expression *in-vivo* (existing PET group plus Dr. Phillips, Psychiatry). The other areas of research are new to our imaging group. They will cover

hypoxia and blood flow in tumour studies (Dr. Durand, BCCA), investigation of type 2 diabetes (Dr. McIntosh, Physiology), brain control on its own sensory input as a function of behavioural and/or spinal cord state (Dr. Soja, Pharmaceutical Sciences), investigation of glycolipid storage disease and *in-vivo* monitoring of enzyme replacement therapy (Dr. Withers, Chemistry and Biochemistry). This research program will bring a larger research community together, thus strengthening and enriching PET imaging at UBC and TRIUMF.