PROBLEMS AND SOLUTIONS ASSOCIATED WITH FACILITY START-UP

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Cyclotron production of radionuclides and positron emission tomography (PET), many believe, has become a sufficiently well developed technology that clinical applications and utility are eminent. The North Shore University Hospital (NSUH) Cyclotron/PET Research Facility was established to advance the transition of Cyclotron/PET technology from primarily a research technique to a clinically useful tool. Detailed here are the problems with the cyclotron and radiochemistry systems, all minor, encountered during the first eighteen months of operation of our laboratory.

The layout of the Cyclotron/PET facility and a description of the equipment installed was presented at the 2nd Workshop on Targetry and Target Chemistry.[1] Installation of the cyclotron was complete in July 1987, and acceptance of the cyclotron, targetry, radiochemistry and ancillary equipment was complete by January 1, 1988. The Senior Radiochemist joined the staff in 1988, completing the start-up staff of six people: Technical Director, Senior Radiochemist, Medical Physicist, Cyclotron Engineer, Nuclear Medicine Technologist, and Administrative Assistant. Coordination with the Clinical requirements of the Hospital is insured by the Clinical Director of the Cyclotron/PET Facility, who also has overall responsibility for the Facility.

The cyclotron continues to operate with a minimum of unscheduled down time. It has proven extremely reliable and the 80-85% proton extraction efficiency is easy to maintain. Most unanticipated shutdowns of the cyclotron have resulted from momentary power failures, which are most frequent in the summer. The original design specifications for this equipment have been upgraded in routine operation. NSUH Cyclotron/PET staff have, in cooperation with Scanditronix, begun development of the MC17F cyclotron for the acceleration of $^{4}He^{++}$ ions. Preliminary data indicate that in addition to protons and deuterons, we will be able to routinely accelerate $^{4}He^{++}$ beams.

Target chambers and precursor compound apparatus associated with the cyclotron have not proven quite as reliable as the cyclotron. The ^{18}F fluoride ion target chamber system has required modification to increase the reliability of product quality and supply. The teflon solenoid valves for control of flow of the target water and helium leaked due to occasional failure of the teflon diaphragm and sticking of the poppet in its seat. Valves from a different manufacturer reduced the failure rate. Teflon plug valves with electrical operators will be installed soon and are expected to provide trouble-free operation.

Teflon tubing, 0.8 mm ID, is used to transport water from the target chamber to the hot cell. After 5 to 15 runs, excessive pressure is required to force the water through the tube. This difficulty was originally attributed to dirt or particulate matter in the target water, but scrupulous cleaning of the target chamber, and care in handling the water have ruled out this possibility.

The original "wafer" design of the target chamber[2] relied on precise machining of the components to provide metal to metal face seals, thereby eliminating elastomer materials which potentially could introduce unwanted organic contaminants into the target solution. The lack of seals, combined with the malleability of the silver target body made it difficult to keep the target free of leaks. Another problem related to the 0.13 mm thick silver disc used as the back of the target chamber recess. Whenever thinning

of the target water occurred, activity was induced in the recirculating cooling water. The activity induced in the cooling water provided an unacceptable source of radiation as it was removed by the ion exchange resins used to maintain the cooling water quality. Increasing the target chamber back thickness to 0.25 mm eliminated this trouble. A new target body incorporating elastomer seals and a 0.25 mm thick back in a single unit will soon be installed.

The first radiolabeled compounds prepared with the cyclotron and utilized in PET studies at NSUH were ^{15}O labeled carbon monoxide, carbon dioxide, and oxygen, administered by bolus inhalation. These compounds were selected because their preparation is simple and they are among the compounds supplied directly from the cyclotron ready for patient use. Using these compounds qualitative imaging with the PET was easily and speedily demonstrated. Quantitative studies await full characterization of the PET and development of expertise in proper blood sampling techniques.

The ^{15}O system performs as originally specified, and is satisfactory for bolus inhalation studies of [^{15}O] labeled gases. Several investigators have requested modification of the system to allow steady state administration of [^{15}O]-CO_2 and [^{15}O]-O_2. By reducing the flow rate of the gases from the processing system and metering them slowly into flowing breathing air while maintaining a high concentration of radioactivity in the process stream, it is expected that a steady state delivery of about 3 to 5 mCi of ^{15}O labeled permanent gas per litre of breathing air can be achieved.

The wide utility of [^{18}F]-2-fluoro-2-deoxy-D-glucose (^{18}F-2FDG) made it an obvious choice as the first compound to be routinely prepared in the Cyclotron/PET Facility radiochemistry laboratory. The Julich method[3,4] for the preparation of this compound was selected, and a technique implemented[5] which has proven reliable and readily adapted to remotely manipulated synthetic procedures. [^{18}F]-2FDG is now routinely available as a radiopharmaceutical from the Cyclotron/PET Facility. The design of a remotely operated [^{18}F]-2FDG preparative system which will be easily automated is nearly complete and construction of the new apparatus is expected to begin by summer 1989.

The second compound selected for production is ^{11}C labeled acetate as sodium acetate in isotonic saline solution. Since the process involves reaction of ^{11}C labeled carbon dioxide with a Grignard reagent, it was expected this would be a relatively straightforward process. Prototype apparatus for the production of [^{11}C]-sodium acetate has been completed and is awaiting modification of the ^{11}C production system. The synthesis of [^{11}C]-acetate developed in our laboratory requires very slow delivery of large amounts of [^{11}C]-CO_2 from the target chamber. Minor modifications to the [^{11}C]-production system and to the procedures for its operations are presently being developed. In early summer 1988 operator error caused a small amount of caustic solution to be sucked into the ^{11}C process delivery line. The incident was not detected for some time and the ensuing problems were difficult to trace. After repair of the damage, a ^{11}CO impurity was observed in the irradiated target gas when it was subjected to GC analysis. The amount of ^{11}CO impurity did not seem related to the amount of oxygen in the target gas, which was varied from <1 ppm to 1%. A CuO furnace is being installed and should eliminate the problem.

A target chamber and production system for the bombardment of high purity neon with a small amount of added fluorine for the production of [^{18}F]-F_2 has been ordered and delivery is anticipated about the middle of May 1989. The first use for this target chamber will be the preparation of [^{18}F]-labeled acetyl hypofluorite to be used in the production of [^{18}F]-6-F-dopa.

Up to 200 mCi batches of nitrogen-13 labeled ammonia are prepared by the reduction $^{13}NO_3$ and $^{13}NO_2$ using DeVarda's alloy, obtained by adding the irradiated target water to a flask containing sodium hydroxide and DeVarda's alloy. The $^{13}NH_3$ is distilled into normal saline to provide a routinely available radiopharmaceutical. The semiautomatic ammonia preparation apparatus provided by Scanditronix was intended for preparation of $^{13}NH_3$ by reduction with $TiCl_3$ and the glassware required modification to

prevent carryover of aerosol from the distillation which alters pH of the product solution. The glassware modification simplified the process and will allow simplifications in the remainder of the apparatus in the future. $^{13}NH_3$ is routinely prepared with the modified apparatus.

The problem of providing a variety of compounds labeled with positron emitting radionuclides for support of a research PET program and developing a significant program of research in nuclear medicine from a 650 ft.^{2} radiochemistry laboratory, using a small staff and maintaining personnel radiation exposure at a minimum, resulted in the development of a strategy in which two small lead hot cells each equipped with a single master/slave manipulator are used to contain portable apparatus specifically designed for a particular synthesis. Criteria for the design of the apparatus included economy, ease of use, simple clean-up and maintenance, and rapid post synthesis clean-up to allow speedy interchange of the apparatus. Prototype apparatus for the [^{18}F]-2FDG preparation and for the [^{11}C]-sodium acetate preparation as well as a simple apparatus for compounding radiopharmaceuticals has been constructed. Each apparatus used disposable pyrogen free, sterile components for containing and manipulating materials. Over fifty 200 - 300 mCi batches [^{18}F]-2FDG have been prepared with this apparatus with practically no difficulty and no hand exposure. The only radiation exposure to the radiochemist occurs during transfer from the hot cell to the pneumatic transfer system of the rabbit containing the syringe of ready to inject [^{18}F]-2-FDG.

A target chamber system for the preparation of ^{79m}Kr, ^{127m}Xe, and ^{19}Ne has been designed and construction is to begin soon. A small bore gas transfer line consisting of a stainless steel and teflon line 3 mm O.D. and 1.8 mm I.D. connects the Cyclotron/PET facility radiochemistry laboratory in the Boas-Marks Biomedical Research Center with the Nuclear Medicine Division about 500 meters distant in the North Shore University Hospital main building. This line was installed specifically for the transport of ^{79m}Kr and ^{127m}Xe, which will be used for continued development of techniques for pulmonary function study.[6]

Detailed above are the few problems encountered since beginning operations in January 1988. All of these problems are minor. The nature of the problems and minimal interference with program implementation demonstrate the maturity of cyclotron/PET technology as a tool ready for clinical application.

REFERENCES

1. Finn, R., Dahl, B., Facility Layout and Planning, Chap. 5 in Proceeding of the Second Workshop on Targetry and Target Chemistry, Heidelberg, West Germany, September 22-25, 1987.

2. Berridge, M.S., Kjelstrom, R., Fluorine-18 Production: New Designs for O-18 Water Targets. Seventh International Symposium on Radiopharmaceutical Chemistry, Groningen, The Netherlands, July 4-8, 1988.

3. Coenen, H.H., Colosimo, M., Schuller, M., et. al., Mild and Effective Aliphatic and Aromatic N.C.A. [^{18}F]-fluorination Using Crown Ether. J. Nucl. Med. 26: 37, 1985.

4. Coenen, H.H., Pike, V.W., Stöcklin, G., Wagner, R., Recommendation for a practical production of 2-[^{18}F]-fluoro-2-deoxy-D-glucose. Appl. Radiat. Isot. 38: 605-610, 1987.

5. Chaly, T., Mattacchieri, R., Velez, J.W., Dahl, J.R., Margouleff, D., A Large Scale Manual Production of ^{18}F Using a Synthetic Unit Made of Sterile Disposable Components and Operated by a Master Slave Manipulator. Accepted for Publication Appl. Radiat. Isot. 1989.

6. Myers, W.G., Dahl, J.R., Graham, M.C., Krypton-79m: A New Radionuclide for Applications in Nuclear Medicine. J. Nucl. Med. 27: 1436-1441, 1986.