THE ARGONNE CANCER RESEARCH HOSPITAL CYCLOTRON

P. V. Harper, M.D., L. S. Skaggs, Ph.D., J. Porter, M.S.
N. Lembares, M.S., H. Forsthoff, E.E., E. Krizek, Ph.D.
K. A. Lathrop, M.S. and F. Kuchnir, Ph.D.
The Argonne Cancer Research Hospital,* University of Chicago, Chicago, Ill. 60637

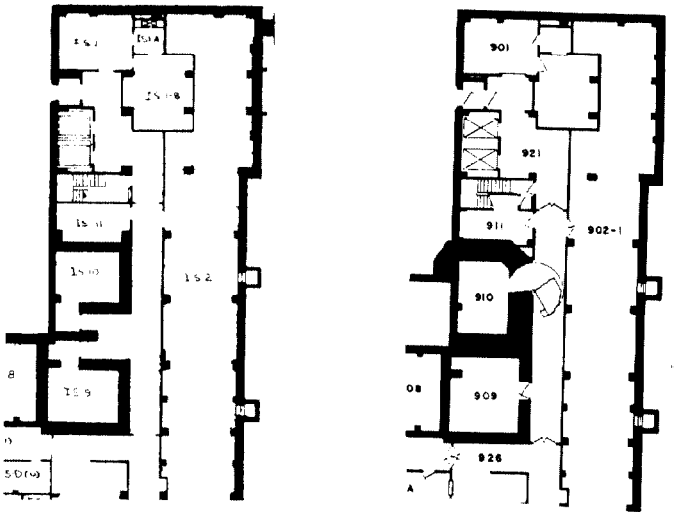
ABSTRACT

The installation of a cyclotron (Cyclotron Corp. CS-15) in an existing building without disruption of other operations was accomplished with relatively little difficulty using overdesigned shielding (6 feet of ordinary concrete). Background measurements on a whole-body counter 50 feet away on the same floor were increased only 10% summing over the whole spectrum. Available space in the vault is 18 x 13 feet, permitting convenient operation of a 3-port target facility oriented vertically. The operating responsibility has been entirely in the hands of personnel without previous experience, with engineering and physics back-up when needed for repairs, maintenance and improvement of the machine. The targetry has been handled almost entirely by the operating staff. During the first three years of operation, down time has been insignificant (~10%), almost equally divided between component failure and operator error. Applications have been in the production of radionuclides for experimental and clinical use. ^{66}Ga and ^{67}Ga were produced by proton and deuteron bombardment of zinc using an internal target. ^{18}F was produced using the $^{20}Ne(d,\alpha)^{18}F$ reaction which proved to be substantially more efficient than the alternative $^{16}O(^{3}He,p)^{18}F$ reaction. ^{13}N as $^{13}NH_3$ was produced by deuteron bombardment of methane as described by Tilbury at Sloan-Kettering. This material has been most useful for imaging the myocardium. ^{111}In, ^{11}C, and ^{15}O are also in production, as well as a number of other nuclides. The possibility of using the deuteron reaction (8 MeV) on beryllium to produce fast neutrons for therapy is currently being explored. In the present configuration, which includes independent control of the harmonic coils, 100 of 160 μA of deuterons have been extracted for this purpose.

*Operated by the University of Chicago for the United States Atomic Energy Commission.

The possibility of obtaining an Argonne Cancer Research Hospital Cyclotron was first considered seriously when we became aware of Cyclotron Corporation activities in 1965. The Nuclear Medicine group at the Hospital had for many years been oriented toward the development of new techniques using radionuclides, particularly for imaging. Excellent facilities in physics, engineering, electronics, radiochemistry, and radiopharmaceutical development were available, as well as a strong clinical nuclear medicine operation. The Physics and Engineering group had developed and operated a 50-MeV linear electron accelerator. Research on imaging had led to the application of linear systems analysis to radionuclide images, and to the optimization of rejection of scattered radiation from the object. Radiopharmaceutical research led to the introduction of ^{99m}Tc into clinical medicine in a variety of forms, and to the development of the reactor production method for ^{125}I. Establishing a cyclotron operation for radionuclide production presented a new challenge, particularly in regard to short-lived positron emitters. Visits to Oak Ridge, St. Louis, and Hammersmith encouraged us to pursue this project.

The architectural considerations of installing a cyclotron in an existing structure without substantial disruption of existing operations, such as the whole-body counter 50 feet down the hall, presented some unique problems. The structure as it originally existed and as it finally evolved is shown in Figure 1. The primary consideration was protection of the whole-body counting facility



Before After

Fig. 1. Floor plans before and after installation of the cyclotron. The original facility had been designed for animal irradiation studies with ^{60}Co.

from irregular background changes while the cyclotron was operating and from gradual neutron activation of the iron-shielded walls and NaI(Tl) crystals. Rough measurements at the Cyclotron Corporation plant with one of the machines bombarding a Be target with ^3He, and using a mock-up to simulate the whole-body counter, led to the conclusion that six-foot-thick ordinary concrete walls and four feet of overhead ceiling should suffice. This amount of shielding far exceeds the requirements for radiation health protection. Subsequent measurements have shown about 10% background increase in the whole-body counter (mostly low-energy) while the cyclotron is operating. The machine available from the Cyclotron Corporation was the CS-15, a 30-inch AVF machine capable of accelerating $^3He^{++}$ to 20 MeV, H^+ to 15 MeV, and D^+ to 8 MeV. The original cost estimate of $500,000 for the entire installation including the machine proved to be almost exactly correct. This cost is of the same order as that of a cardiac catheterization laboratory, and is far lower than the cost of a conventional neuroradiology facility. Thus, the expense of a cyclotron facility is far from unthinkable for a medical complex.

Training of our staff consisted of brief visits by senior personnel to various medical cyclotron installations, and the assignment of one medical physicist to the ANL Cyclotron Facility for familiarization with principles of target construction, handling, cooling, and processing. Experience with the operation of the machine was acquired during the four-month period of installation and testing. At the end of this time performance specifications for our cyclotron had been met (50 μA extracted beam for 7-1/2 hours with H^+, D^+, and $^3He^{++}$). During the period of testing, almost everything that could go wrong with all of the various systems involved in the machine did go wrong. This was most instructive, for it enabled the engineering staff to become quite secure in handling all categories of problems.

The operating personnel for the first three years was limited chiefly to the users of the machine, i.e., the senior author and one medical physicist. During this time a few installation errors surfaced. The heating unit of the diffusion pump had apparently been damaged in shipment, so that it was no longer in contact with the vessel. It thus operated hot and finally burned out, causing a three-week shutdown. The first ruptured exit foil disclosed that the anode power high vacuum cut-off relay had never been connected. This led to a disastrous arc in the oscillator which perforated the oscillator tube envelope. One of the D's began to leak water and was promptly replaced under the warranty. Before stable operation could be restored with the new component, a minor design change in the anode power supply keeping the feedback loop in the voltage control closed at all times, became necessary. The only other major component failure has been the breakdown of the oscillator anode tuning capacitor which required replacement. Improvement of the insulator design in the ion source has eliminated most of the difficulty from improper arcing.

Cooling water for the machine was provided by a recirculating system with a deionizer and heat exchanger. This has proved most satisfactory, the conductivity being maintained consistently at about one micro mho/cm.

During the three years of operation, the transport system for the extracted beam has been built up in stages. The first includes a steering magnet constructed from a one-HP motor stator that can bend the beam 2 to 3 degrees in either direction. This is necessary because different particles are extracted at slightly different angles, which vary slightly from day to day. Next is a watercooled pneumatic shutter, then a double-vane Danphysik beam monitor which sweeps across the beam, displaying X and Y profiles. This is followed by a 3-position 15° switching magnet oriented vertically, leaving approximately 5 feet for targetry beyond the exit ports. As it leaves the machine, the beam is strongly focused in a vertical plane and can be carried without loss through 5 feet of 1-7/8" beam pipe without additional focusing. An extraction efficiency of 50 to 60% is routinely achieved; this has been further improved by the use of independent power supplies for each of the three harmonic coils. 100 of 160 μA of deuterons have been extracted recently. The limiting parameter in extracted beams is nominally one kilowatt of power dissipated in the extractor assembly.

As quarters are rather close in the cyclotron vault, it has become routine practice to limit the amount of radioactivity handled to modest levels (< 50 mCi). This would not be possible if we were producing materials for institutions in addition to our own. In general, we have used gas targets whenever possible because of the associated low power density and consequent ease of cooling. This has been possible with ^{18}F, ^{11}C in various forms, ^{13}N, and ^{130}Cs. A horizontal target on the lower port causes the beam to be incident at a grazing angle of 15°, spreading out the beam which is somewhat defocused in the horizontal plane by the specially designed switching magnet pole face. This spreading makes possible the use of targets which are easily melted, such as metallic thallium. Easily cooled metallic targets are used in a conventional configuration normal to the beam, with cooling water running across the back of the target foil in a thin film. Double foils separated by a layer of helium for cooling, circulating in a closed circuit, have been used with high proton currents (30-50 μA). When it is convenient or necessary to secure a high beam current, an internal target electroplated onto a flattened copper tube is used.

The materials which are being produced routinely or with the thought that their production might ultimately become routine are: 1.7-h ^{18}F, 9.5-h ^{66}Ga, 78-h ^{67}Ga, 10-min $^{13}NH_3$, 20-min ^{11}C as CO, CO_2 or CN, 2-min ^{15}O, 52-h ^{203}Pb, 48-min ^{49}Cr, 36-d ^{127}Xe, 2.8-d ^{111}In, 67-min ^{110}In, 30-min ^{130}Cs, and 12-d ^{202}Tl.

The principal reactions for the indicated above nuclides are shown in Table I, with production parameters.

Briefly, the procedures used for each material are as follows: 78-h gallium-67. This material, when administered in carrier-free form as the citrate, localizes well in many malignant tumors which can then be imaged with proper equipment.[1] This application was first discovered by the Oak Ridge group, which used the material produced on the 22-MeV proton cyclotron from a zinc target. This method has the disadvantage that large amounts of 9-h ^{66}Ga are also produced; this must first be allowed to decay. In exploring the

Table I Production parameters and approximate yield*

Product	Target	Particle	Reaction	Beam Current (μAh)	Yield / μAh	Remarks
^{18}F	^{20}Ne	8-MeV D^+	d,α	8	16 mCi	
^{66}Ga	^{66}Zn	15-MeV H^+	p,n	50	7 mci	Internal target
^{67}Ga	^{66}Zn	8-MeV D^+	α,n	200	30 μCi	Internal target
^{13}N	^{12}C	8-MeV D^+	α,n	8	40 mCi	Flowing CH_4 target
^{11}C	^{14}N	15-MeV H^+	p,α	20	105 mCi	
^{15}O	^{14}N	4-MeV D^+	d,n	10	350 mCi	
^{203}Pb	^{203}Tl	15-MeV H^+	p,n	15	70 μCi	Horizontal target
^{49}Cr	^{48}Ti	20-MeV $^3He^{++}$	^3He,2n	1	8 mCi	
^{127}Xe	^{127}I	15-MeV H^+	p,n	20	80 μCi	Horizontal target of NaI
^{111}In	^{111}Cd	15-MeV H^+	p,n	20	1 mCi	
^{110}In	^{107}Ag	16-MeV $^4He^{++}$	α,n	20	250 μCi	Internal target
^{130}Cs	^{130}Xe	15-MeV H^+	p,n	20	6 mCi	
^{202}Tl	^{202}Hg	15-MeV H^+	p,n	15	10 μCi	Mercury metal target

*Saturation activity/average life

various reactions for making ^{67}Ga on the CS-15, we found that the 8-MeV deuterons on zinc yielded about 30 μCi per μAh, and that no ^{66}Ga at all was produced.

We used an internal target consisting of a flattened 1/2-inch copper tube with the zinc electroplated onto the exposed surface. This was placed in the machine at a radius of 12-1/2 inches, with the target surface facing the beam at an angle of 10° to the tangent. By proper adjustment of the harmonic cells, the beam could be steered to a grazing incidence. Routinely, 200 μA and occasionally up to 400 μA could be tolerated by the target without burning. A critical factor in target preparation appeared to be smoothing and compacting the rather spongy layer of zinc with a burnishing tool several times during the electroplating process. This improved the thermal conductivity of the zinc layer, which was ~ 5 mils thick. The wall thickness of the copper tubing was 20 mils. A water flow of 2-3 gal/min was maintained. The surface area of the bombarded region was ~ 2 x 20 mm, giving a power density of 4 KW/cm^2 at 200 μA. An attempt was made to increase the effective target area by oscillating the

target vertically through a distance of 5 to 6 mm. However, a frequency of only 10 cycles/sec could be achieved without substantial redesign of the target, and it was never established whether the oscillation was helpful.

The product was separated from the target by dissolving the zinc plate off the copper tubing with HCl, extracting into isopropyl ether from 7.7 N HCl, and back-extracting with 2 N HCl. The back extraction was necessary because the oil vapor from the diffusion pump which permeated the target was left behind in the organic phase of the extraction. This operation was carried out on a routine basis once a week for almost three years, and has recently been abandoned as ^{67}Ga has become readily available from commercial suppliers. (The Medi-Physics Group, using an enriched Zn target, has extended this source reaction to commercial use.) The use of ^{67}Ga injected intravenously as the citrate is illustrated in Figure 2.

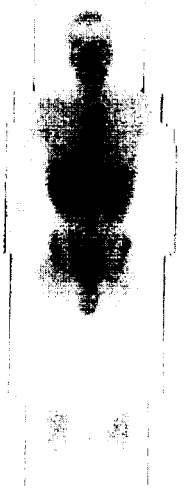


Fig. 2. Abnormal localization of ^{67}Ga injected intravenously as citrate is shown in chest of patient with Hodgkin's disease

9-h ^{66}Ga was produced using the same targetry as for ^{67}Ga with an internal proton beam. Gallium-66 was used with ^{67}Ga in double-label studies of the biological localization in animal tumors of carrier-free gallium in different chemical forms.

2.8-d ^{111}In. Like gallium, 2.8-d ^{111}In localizes in tumors. This nuclide was produced by proton bombardment of cadmium in the external beam. The chemical separation presents no difficulties.[2] This material has also been used for animal studies in placental localization, when longer time intervals were needed than could be accommodated with generator-produced ^{113m}In (115-d ^{113}Sn → 1.7-h ^{113m}In).

1.7-h fluorine-18. This agent used as the fluoride is one of the best materials for imaging bone and bony lesions. It can be reactor-produced, though not efficiently; the existing accelerator methods are the (α,2n) and (^{3}He,n) reactions on ^{16}O as a water target. Because of our concern about the danger of water entering the machine due to foil rupture, we were led to explore other possible reactions. To our surprise, at the energies available to us, the d,α reaction on ^{20}Ne (90% abundance) proved to be substantially more efficient than the ^{16}O(^{3}He,n)^{18}F reaction, and had the additional advantage of permitting the use of a gas target. The fluorine-18 product was deposited on a Pyrex glass liner of the target chamber and could be recovered efficiently by washing the liner with sterile

0.9% NaCl solution, so that it was ready for immediate use. We have used this method routinely for 2-1/2 years, producing 15- to 30-mCi batches of activity once or twice a week as needed for our clinical operation. Recently this procedure also has been abandoned because of the ready commercial availability, in massive quantities, of ^{18}F produced by the same reaction.

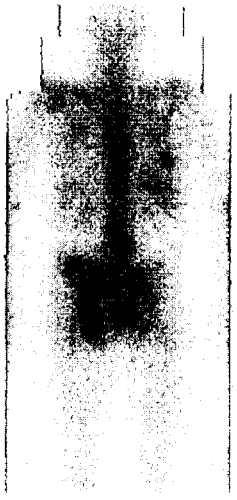


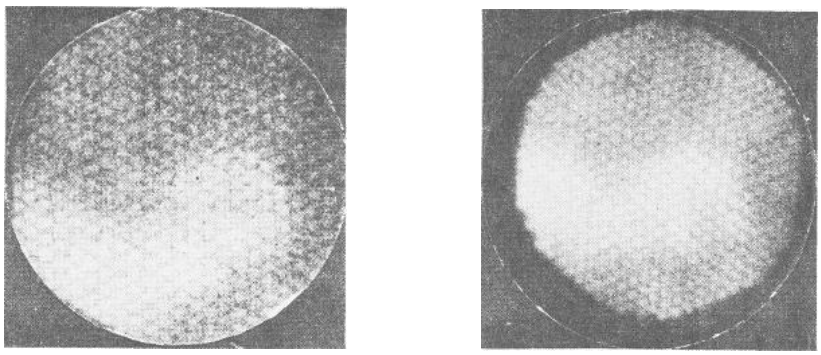
Fig. 3. ^{18}F bone scan of patient with tumor involvement of left pelvic bones and right ribs.

10-m nitrogen-13 has been produced during the past year by the method described by Tilbury et al.,[3] at the Sloan-Kettering Institute which also has a CS-15 cyclotron. Methane gas flowing through a target chamber at several l/min is bombarded with 8-MeV deuterons, and the gas leaving the target chamber is bubbled through sterile 0.9% NaCl solution. The product, which is mostly in the form of $^{13}NH_3$, dissolves in the solution and is available for immediate use. A number of radiochemical impurities (15-20% of the total activity) are removed by passing the gas through an absorbent column of soda lime and one of siliconized glass wool cooled to dry ice temperature, so that a 97-98% pure product is available. Batches of 20-30 mCi can be prepared in this manner. The ^{13}N in the form of NH_3 is useful particularly for myocardial images when injected intravenously.[4] The high-energy radiation, 511 KeV, is difficult to image well with conventional equipment but, if used with a special tungsten collimator, a conventional Anger camera is very effective in producing excellent myocardial images with a small radiation dose to the patient. Prepared in this way, ^{13}N has also been used as a substrate for enzymatic synthesis of glutamate; besides, it can be decomposed by hypobromite to yield free $^{13}N_2$ gas for pulmonary studies.

20-m ^{11}C is being produced by the (p,α) reaction on nitrogen-14. 500-mCi quantities may be produced without difficulty and may be converted to CO_2, CO, or CN^- as desired by on-line processing while being transported to the high-level handling facilities. A large variety of potential uses for these materials exists for physiologic studies and chemical syntheses.[5-8]

2-m ^{15}O produced by (d,n) reaction on ^{14}N is likewise available for physiologic studies. It has been produced in 250-mCi batches.[9,10]

52-h ^{203}Pb decays by electron capture largely via the 279-KeV level. It emits the same gamma as the commonly used ^{203}Hg, but is free from the primary-particle radiation and long half-life of the latter.



(a) (b)

Fig. 4. Normal (a) and abnormal (b) heart images made with $^{13}NH_3$. The image on the right shows a large inferior defect due to a myocardial infarction.

Experimental studies indicate that this material may be useful for visualizing the cerebrospinal fluid compartments. Production by proton bombardment of metallic thallium is practical for experimental quantities of the material, but probably is not efficient enough for routine clinical use with our machine.[11]

32-d ^{127}Xe likewise has been produced by proton bombardment of an iodide salt in quantities sufficient for experimental purposes. It appears to be greatly superior to reactor-produced ^{133}Xe for pulmonary-function and imaging studies. The long physical half-life of ^{127}Xe causes no biological difficulty because of the rapid excretion of the inert xenon gas. Both ^{127}Xe and ^{203}Pb should be easy to produce in the high-energy, high-current proton beams available at Brookhaven and Los Alamos.[12]

42-m ^{49}Cr has been produced in $\sim$ 50 mCi quantities by $^{3}H^{++}$ bombardment of titanium. This material would be extremely useful as the chromate for labeling the circulating blood elements--erythrocytes, leucocytes and platelets--for a variety of purposes. The reactor-produced ^{51}Cr has too long a half-life for many of the possible applications in this field. The chemical problems of the separation of this material from the titanium target as chromate in a form suitable for administration to humans is still under study.

One of the great difficulties in human radionuclide distribution studies is to determine accurately the fraction of the injected dose of a preparation present in a particular organ. The use of positron annihilation radiation detected in coincidence eliminates the effects of attenuation in tissue, since the combined path length of the annihilation pair in tissue is constant. In addition, the effects of scatter are eliminated except for chance coincidence. Thus, when quantitation is necessary, it is desirable to utilize positron-emitting isotopes of nuclides in common use in nuclear medicine.

The specific localization of indium ion in the placenta has been clearly demonstrated in the mouse and rat.[13] Documentation of the time course of this phenomenon in the living healthy human, using innocuous levels of radiation, appears desirable. For this purpose, 67-m ^{110}In, a β^+ emitter, was produced to permit the best choice of indium isotope (^{113m}In, ^{115m}In (both generator-produced) or ^{111}In), by (α,2n) reaction on silver-107 at the 16-MeV energy available to us. There was virtually no contamination with the 2.8-d ^{111}In, and the existing separation methods are quite practical.[14] The targetry used was similar to that with ^{67}Ga. The copper tubing was first plated with gold to protect the copper from acid and then with the silver target material. The 30-m ^{130}Cs, a β^+ emitter, is being produced for this same type of study by proton bombardment of xenon gas. Ninety-five percent of the induced activity at the end of bombardment was the ^{130}Cs. The reduced uptake of Cs by malignant tumors has been used successfully as a criterion of the efficacy of chemotherapy; ^{131}Cs has been used in this way on superficial lesions.[15] Extension of the method to deep lesions may be possible using coincidence positron detection with ^{130}Cs. The target for production of ^{130}Cs was similar to the ^{18}F target with an aluminum liner from which the ^{130}Cs could be recovered easily by washing.

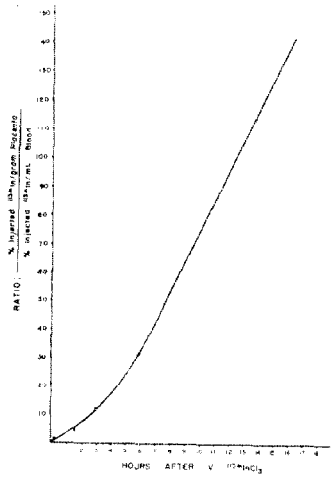


Fig. 5. Specific uptake of indium by mouse placenta.

Thallous ion, Tl^+, acts in the body very much like K^+ ion. Experimental studies with the mixture of thallium nuclides produced by proton bombardment of mercury have confirmed this, and have shown that thallium nuclides are also potentially very useful materials for myocardial visualization (Fig. 6). To produce clean thallium nuclides is beyond the capability of our machine. The group at Brookhaven[16] has used the reaction ^{203}Tl(p,3n)^{201}Pb. The concurrently produced 3-h ^{202}Pb is allowed to die away, and the remaining 9-h ^{201}Pb is separated from the thallium target and then allowed to decay to 74-h ^{201}Tl. This decays by electron capture and emits only mercury X rays and a 167-KeV gamma ray. It thus has a reasonable half-life and emits no primary-particle radiation, so that the radiation absorbed dose is small.

Production of substnatial amounts of activity by these reactions is not possible with the CS-15 machine. A similar reaction that would be desirable is ^{127}I(^{3}He,3n)^{127}Cs. This 6-h material

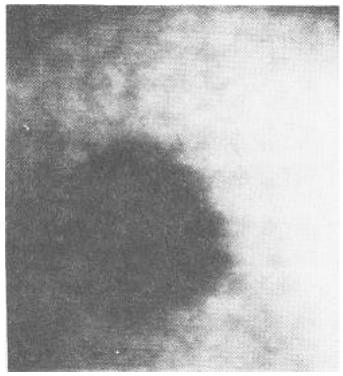


Fig. 6. Myocardial scan using mixture of Tl^{+} nuclides produced by proton bombardment of mercury.

would be very useful, as would 7.2-h ^{73}Se produced from arsenic-75 by (p,3n). The limitation on the production occasionally causes regret that we do not possess one of the larger machines.

One further application for which a higher-energy machine would be desirable is in the production of fast neutrons for therapy. Encouraged by the experience of the Hammersmith group, we have undertaken a study of the feasibility of using the CS-15 as a neutron source. The general conclusion appears to be that a serious experimental trial is justified. The possibility of such an application was considered in the original architectural plans. The detailed feasibility study is presented in the report by Drs. Kuchnir, Skaggs et al. in these proceedings.

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