BNL-41257
CONF-8809261--1

CYCLOTRONS FOR CLINICAL AND BIOMEDICAL RESEARCH WITH PET

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BNL--41257

DE88 009692

The purpose of this commentary is to present some background material on cyclotrons and other particle accelerators particularly with a view toward the considerations behind acquiring and installing such a machine for purely clinical and/or biomedical research use.

At present there are approximately twenty-eight institutions in North America with accelerators primarily used in conjunction with PET (cf. Table 1). At the present rate of growth, well over 50 such centers should be in existence in North America by 1990. It is also apparent that a number of centers are being developed in which a PET machine is installed without being coupled to an on-site cyclotron facility. Such centers will depend on generators such as the ^{82}Sr-^{82}Rb generator and fluorinated compounds from production centers.

The particle accelerator is simply a source of reagents, protons and deuterons which are used to bring about the desired nuclear reactions yielding positron emitters or other radionuclides. Alpha particles and helium-3 ions are also of some interest but do not have any importance with regard to radionuclides for PET.

Cyclotrons

A cyclotron can be considered as being composed of several basic components, an ion source which provides the ions to be accelerated, an RF power source which provides the energy needed to accelerate the ions in a specially constructed vacuum chamber, a magnetic field which controls the position in space of the ions and an extraction system which allows one to remove the accelerated ions from the body of the machine. Such a simplified viewpoint does not do justice to the complexities of a cyclotron but should aid in understanding its basic operating features. The mechanism of extraction in a negative ion machine does not require the conventional septum-deflector system of a positive ion machine (vide infra).

The magnetic fields in medical cyclotrons are in the 1.5 - 1.9 Tesla range but can be higher as in the new superconducting cyclotrons. Some simple equations can be used to appreciate cyclotron principles. The kinetic energy of the emerging particle must be such that the thresholds for the nuclear reaction required are exceeded sufficiently to allow reasonable production of radionuclide. The equation which governs this energy is (eq. 1)

$$T = \frac{47.84\ B^2 r^2 q^2}{M} \qquad \text{Eq. 1}$$

where B is the magnetic field in kilogauss, r is the radius of the outermost orbit, q is the charge of the particle, M is the mass of the particle in AMU, and T is the kinetic energy in eV. It is easily seen that in a two particle machine the kinetic energy of the deuteron, i.e. M=2, will be half that of the proton, thus a 16 MeV proton machine can deliver 8 MeV deuterons. However, some adjustments in design parameters can raise the relative deuteron energy. The radiofrequency f in megaherz eg. for protons is given by eq. 2 where B,q and M are as defined above.

$$f = \frac{1.52\ Bq}{M} \qquad \text{Eq. 2}$$

Modern cyclotrons are isochronous which means that they are designed to make the ions revolve at constant frequency and by varying the magnetic field (AVF, azimuthally varying field) the maximum energy achievable for the particle could exceed that imposed by the design of a "classical" cyclotron. In the classical machine as the relativistic mass increases the frequency of ion rotation decreases until the ions are no longer in phase with the change in sign of the accelerating voltage at the gap between the dees, (vide infra) and the ion no longer can accelerate. This limiting energy is around 25 MeV.

In any cyclotron the ions are introduced from an ion source which injects either a positive ion such as a proton or a negative ion eg. H^- at the center of the machine at a point in the gap between the dees (dees are copper chambers which in early cyclotrons were composed of two semicircular hollow chambers facing each other as "D" hence dees or "D's". (Dees in modern machines are no longer semicircular but can be 45°, 90°, etc. sectors). The ions are accelerated towards the dee with a given potential. Once inside the dee the ion velocity remains constant because of the electrical shielding of the dee but the orbit of the ion is circular due to the magnetic field at right angles. The radius, R_1, of this orbit is given by eq. 3 where m is the mass of the ion and V_1 the velocity of the ion. B and q are as above.

$$R_1 = \frac{m\ V_1}{Bq} \qquad \text{Eq. 3}$$

As the ion enters the gap between dees the voltage has reversed and the ion is again accelerated and the radius of the orbit is now given by eq. 4

$$R_2 = \frac{m\ V_2}{Bq} \qquad \text{Eq. 4}$$

Thus the ion spirals out from the center of the machine. The oscillation frequency is adjusted to the property of the specific ion and strength of the magnetic field so that particles are in phase with change in potential across dees.

In a positive ion machine, i.e. one which accelerates H^+ the ions are removed from orbit by a combination of electrostatic deflector at high negative potential and a magnetic channel which helps to focus outgoing ions. These ions then pass through a window (a thin metal foil) which isolates the necessary high vacuum in the interior of the cyclotron. Further shaping and manipulation of the beam is possible before the beam enters the target gas or other material. The beam current is limited by the nature of the ion source and its capabilities and the extraction efficiency of the particular machine. However, it should be noted that the beam currents deliverable by all currently available medical cyclotrons are in excess of normal needs.

In a negative ion machine the H^- ion is passed through a foil, usually carbon, in which the two electrons are stripped off. The proton which emerges finds itself in the same magnetic field whose direction kept the negative ions in circular pathways. Positive ions are also constrained to a circular pathway by the same magnetic field but the direction would be opposite to that of the negative ion thus they would be caused to bend out and leave the machine. A septum deflector is therefore not necessary.

The advantages and disadvantages of positive and negative ion machines will not be addressed in this paper. There is little doubt that both positive and negative ion machines can produce the needed radionuclides. While many factors influence the amount of radionuclide that can be produced, the basic limiting factors are the energy of the proton and the available current. Virtually all currently offered small medical cyclotrons provide nearly the same external beam current but the particle energies are different from different manufacturers. Table 2 lists those machines currently available.

Table 2

Machines with energies larger than 17 MeV protons are not detailed here [(1) Wolf, A.P. in Medical radionuclide Imaging IAEA Symposium Series, Los Angeles 1976, IAEA Vienna (1977) Vol. I, pp. 343-353; (2) Wolf, A.P. and Jones, W.B. Radiochim. Acta 34, 1-7 (1983)], but some general comments are in order. Radionuclides such as gallium-67, iodine-123, krypton-81m thallium-201, etc. cannot be produced in usable amounts with 17 MeV machines. Cyclotrons in the 30-40 MeV proton energy range are required. With the advances in cyclotron technology of the past few years however, these larger machines deserve some consideration. They do require more power, more shielding and more space, but are only marginally more difficult to operate. In recent years the use of xenon-124 in the nuclear reactions $^{124}Xe(p,pn)^{123}I$ and $^{124}Xe(p,2n)^{123}Cs \rightarrow {}^{123}Xe \rightarrow {}^{123}I$ has made high purity ^{123}I easily accessible by production on 30 MeV machines. Indeed the radionuclidic purity of the iodine-123 is not matched by any other production method. Thus a 30 MeV machine could provide radionuclides for clinical nuclear medicine application.

Ref. 1 & 2

Strontium-82 required for the ^{82}Sr-^{82}Rb generator requires considerably higher energies and currents for efficient production and therefore is unavailable from either 17 or 30 MeV machines.

There are three other types of accelerators which can be considered.

The Van de Graaff accelerator has been used in some institutions to produce small amounts of radioisotopes for research purposes. There is however no manufacturer this author is aware of who has produced a high energy high current machine for radioisotope production. It is unlikely that such a machine would be competitive with currently offered cyclotrons.

The Linear accelerators or Linacs are a possibility. Machines for isotope production have been announced but none have at this writing appeared on the market.

A Superconducting small cyclotron has been announced (cf. Table 2) but at present nothing is known about general operating characteristics and reliability. Such a device is however intriguing in that it represents a decrease in size but especially in weight.

Practical Considerations

Machine Peripherals

Purchase of any machine whether it be a cyclotron or any other device must always include a clear statement of what the purchase price includes. Basic items such as power supplies, primary cooling system, auxilliary control devices and control console are a necessary part of the machine. However, in order to have an operating system such items as targets, target changers, focussing magnets, collimators, beam pipes and switching magnets (should multiple lines be required on a positive ion machine) also need to be considered. Depending on the infrastructure available at the institution such items as targets and collimators can be designed and built in-house but not necessarily at a reduction in cost.

All machines currently available have some degree of computer control or are indeed menu-driven as to selection of beam energy, current, choice of target and beam on beam off schedule. The level of control and additional cost, if any, also varies.

Going beyond the actual cyclotron hardware one might consider the acquisition of radioisotope and labeled compound production devices from the manufacturer. In developing a labeled compound synthesis capability, the basic feature is the production of precursors for synthesis. A list of the most commonly used precursors is given in Table 3.

Table 3

The literature is repleat with descriptions of devices for preparation of these compounds. However most cyclotron manufacturers offer a precursor synthesis package which allows automated preparation of most or all of the precursors listed in Table 3. Inclusion of such a package is a wise addition to the overall purchase.

The final consideration in the acquisition of a cyclotron unit is what one does about the production of radiopharmaceuticals. It is here that one needs to consider the needs of the PET program most carefully. There are perhaps three scenarios: (1) purely clinical use, (2) some research and clinical use, and (3) an extensive program in clinical and biomedical

research. Each of these scenarios requires a different approach. Let me address (1) and (3). If routine clinical use is contemplated then automated production of radiopharmaceuticals is a necessity. The organization in question must then depend on the availability of "black boxes". The synthesis of ^{18}F-FDG is available by automated black boxes from virtually every manufacturer of cyclotrons as is the preparation of all of the oxygen-15 compounds needed for blood flow studies, etc. However, beyond that, only a few of the manufacturers offer a fairly comprehensive catalog of black boxes as shelf items. The impression that one can hire a technician to prepare new compounds as they appear in the literature in a 200 ft^2 laboratory is not worthy of comment here. Thus where purely clinical use is contemplated, careful assessment of purpose and facilities is necessary.

When a broadly based program in clinical use, clinical research and basic biomedical research is contemplated, then the full interdisciplinary and multidisciplinary capabilities of the institution need to be considered. The infrastructure needed to support such an effort goes well beyond what might be needed in a purely clinical setting.

A final note on "black boxes" for synthesis concerns quality control. The sterility and apyrogenicity to say nothing of radionuclidic, radiochemical and chemical purity of the compound is not addressed as a guarantee in the commercial devices currently available. Thus the institution must develop a system of analytical control in-house. Such protocols could be assigned to the hospital radiopharmacy or set up as a separate function in the cyclotron complex.

Another aspect is what one expects of the capabilities of the machine. Table 4 lists the most common nuclear reactions in use today.

Carbon-11 is readily produced whether one has a proton only or a proton deuteron machine. The boron reaction once widely used is used in only a few places today. The remaining radionuclides require enriched isotopes if a proton only machine is available but enriched isotopes are unnecessary if a two particle machine is installed. It should be noted however that the convenience and high yield of the ^{18}O(p,n)^{18}F reaction makes this reaction most attractive if one requires large quantities of fluoride ion in a no-carrier-added (NCA) state. It should also be noted that the oxygen-15 production reaction is more conveniently and cheaply accomplished with the ^{14}N(d,n)^{15}O reaction. It is not the intention of this paper to go into detail on one versus two particle machines nor what is the optimum energy for particles. There is a great deal to be said on both sides of this viewpoint and must be left to be decided by the needs and interests of the buyer.

Table 5 gives a comparison of thick target yields as a rough guide for those interested in this question but again caution must be used in considering such data since there is more to the question of energy and yield versus actual radionuclide production capability.

Siting

A Cyclotron including shielding regardless of whose manufacture, concentrates a great deal of weight in a small space. In this writers opinion, on-grade installation is mandatory. Ideal is a space below ground

such as a corner of a building where two sides are surrounded by earth. The question of shielding a cyclotron is also beyond the scope of this paper, but some general concepts can apply. All cyclotrons require shielding due to radiation of various types emanating from the machine during particle acceleration. There is no such thing as a self-shielding machine. What is meant when this term is used is that an auxiliary shield can be provided that covers the machine rather than placing the machine in a shielded vault. Partial self-shielding of a machine where the yoke of the machine is folded over and covers the dee vacuum chamber is a design feature of some machines. Nevertheless, shielding is necessary. The amount of shielding and placement of the shield is a function of available space, local regulatory radiation safety requirements and convenience in using and servicing the machine. If an auxilliary shield is not offered with the machine, walls of ordinary concrete or concrete blocks, a minimum of one meter to a maximum of two meters thick, are necessary. Pneumatically operated doors are not needed (depending on local codes) a maze will do or in the case of auxilliary shields, an adequate (safety interlocked) enclosed space is necessary where the distance from the center of the machine to where personnel are located to allow safe working conditions (again depending on local health physics rules and local codes) is well defined and adequately monitored.

The machine, if possible, should be placed with the external beam part of the machine pointing at the most heavily shielded portion of the room, eg. a corner of a basement. Room sizes will vary depending on whose machine one buys and what space is available. Space for power supplies, primary cooling system and control room must also be available.

Service

This will obviously vary from manufacturer to manufacturer. It sould be an absolute necessity especially in the case of a purely clinical facility that rapid response to need for service be provided. Some of the manufacturers now offer yearly maintenance and service contracts, and to this authors knowledge, are thououghly reliable and prompt. It is our experience that cyclotron down time is minimal and generally does not exceed about 5% of total operating time.

A contrast between cyclotron and PET machines can be made. PET machines are constantly evolving and sensitivity and resolution are slowly approaching what is possible for PET thus technical obsolescence in a currently purchased PET is perhaps 5-8 years. A cyclotron is basically forever. While increasing automation is offered every few years as is increasing sophistication in design, a machine purchased today will allow production of more than needed radionuclides as far into the future as one can foresee viable programs and needs. The BNL 60-inch cyclotron has been in operation for forty years and one can expect the BNL medical cyclotron (JSW) to be in operation for an equally long period.

Operations

Some Cost Factors to be Considered

This is a minefield for a scientist not trained in the fine points of cost analysis, amortization, etc. that must be considered is setting up a PET center. However, the following analysis is offered as a very rough guideline to the purchaser and is based on the assumption that the machines are not purchased outright and facilities are not donated philanthropically.

Cost of Operating a Medical Cyclotron-PET

(1) The estimate given here is based on the following assumptions. A basic investment of about $\$1.4 \times 10^6$ 1987 dollars which includes installation, target systems, a basic precursor system, depreciation and interest payments over 10 years based on one payment/year at 10% interest; operating costs which include a technician and a professional plus fringe benefits, materials, supplies, travel, including overhead on all applicable items, power costs and a maintenance contract. At the present time, this cost will be $500,000 to $550,000/yr.

(2) The cost of the radiopharmaceutical is based on 2000 FDG patient runs/yr and includes cost of supplies, chemicals, etc., a technician to produce FDG including fringe, the FDG black box at 10% interest depreciated over five years, the total being $175,000/yr.

(3) The cost of PET covers three scenarios depending on the initial cost of the PET and is calculated for a PET at $\$2 \times 10^6$, $\$1.5 \times 10^6$, or $\$1 \times 10^6$, payment over five years at 10%, medical supplies per patient, operating personnel plus fringe and maintenance on PET plus overhead on all applicable items. The totals for each become $\$1.1 \times 10^6$, $\$0.94 \times 10^6$ and $\$0.76 \times 10^6$ per year.

(4) Thus the cost/patient considering items (1), (2) and (3) using FDG only and 2000 examinations/yr comes to:

Total Cost/Patient

(1)	Cyclotron(max)	275	275	275
(2)	Radiopharmaceutical	88	88	88
(3)	PET	550	470	380
		$913	$833	$743

Not included in these very rough estimates in 87-88 dollars and under the specified circumstances are the cost of the physician, nurse, medical support not included in overhead, professional data analysis, development and installation of facilities for a new labeled tracer and profit.

Given these assumptions it is clear that the PET is the single most expensive unit of this analysis especially as five years instead of ten were used for depreciation. In any event, one can manipulate such cost analyses in many ways but economical operation of PET in a clinical environment requires a

reasonable patient throughput. Eight patients/day on FDG, more could be done if oxygen studies alone are used, is reasonable in our experience but it does require careful scheduling and efficient operation.

Radiopharmaceuticals

What is possible here is certainly outside the scope of this paper. A guide to what is available today [(3) Fowler, J.S. and Wolf, A.P. The Synthesis of Carbon-11, Fluorine-18 and Nitrogen-13 Labeled Radiotracers for Biomedical Applications, Nuclear Science Series, Natl. Acad. Science, National Research Council (Monograph) pp. 1-124 (1982) NAS-NS-3201] can give the interested reader a view of the scope of labeled radiopharmaceuticals. Suffice it to say that to make profitable ^{18}F-FDG, the oxygen-15 labeled gases, ^{11}C and ^{18}F labeled neuroleptics, ^{11}C and ^{18}F labeled tumor agents and ^{11}C and ^{18}F labeled fatty acids on a routine basis considerably more than a few black boxes is required. The level of radiopharmaceutical production to say nothing of research on new compounds must be guided by the demands of the program and the personnel that can be provided in support of such a program.

ref. 3

Personnel

Here again one is faced with decisions based on the size of the infrastructure already in place in the institution and the size and demands of the contemplated program including taking into account such "mundane" things as vacations or illness of operating personnel.

Focussing on the operation of the cyclotron alone, a minimum of two people is required for a full scale program. Depending on local requirements, three may be a minimum if the code requires two individuals to be present at all times due to health physics rules. If in-house maintenance is contemplated, certainly two to three individuals are necessary. Cyclotron operation has not as yet reached the stage where easy interchange of trained professionals is possible as might be the case in operating a hospital x-ray unit.

Conclusion

A cyclotron properly maintained can provide useful service for many years. As a source of positron emitting radionuclides it suffers none of the disadvantages of long term activation of components of the machine nor of storage and disposal problems for the compounds themselves. The efforts by manufacturers to increase reliability and simplicity of operation has certainly been fruitful. Indeed it is now within the realm of possibility to charge targets and begin bombardment from a home based PC and modem so that the radionuclide is ready for use on arrival at the place of work.

This author would hope that such automation will ultimately involve radionuclide production, radiopharmaceutical synthesis and analytical control from a single menu-driven computer thus making the radiopharmaceutical as readily available and on demand as a drug from a hospital pharmacy. This feature can be expected to become a reality in the foreseeable future.

Being able to study human biochemistry and physiology in normal and pathological states and the benefits to be derived therefrom in terms of new

basic information on the human condition and the unique diagnostic capabilities possible make cyclotron-PET one of the most exciting new tools for basic research and diagnosis in the human health area.

Acknowledgement

This work was carried out at Brookhaven National Laboratory under contract DE-AC02-76CH00016 with the U. S. Department of Energy.

Table 1. Research and Clinical Positron Production and Imaging Centers in North America[a] (1987)

Baylor University, Waco, Texas
Brookhaven National Laboratory, Upton, New York
Case Western Reserve, Cleveland, Ohio
Duke University, Durham, North Carolina
Johns Hopkins University, Baltimore, Maryland
McMaster University, Hamilton, Ontario, Canada
Massachusetts General Hospital, Boston, Massachusetts
McGill University, Monteal, Quebec, Canada
M. D. Anderson Hospital, Houston, Texas
Mt. Sinai Hospital, Miami Beach, Florida
National Institutes of Health, Bethesda, Maryland
North Shore University Hospital, Manhasset, New York
Oak Ridge National Laboratory, Oak Ridge, Tennessee
Sloan Kettering Cancer Center, New York, New York
TRIUMF, Vancouver, British Columbia, Canada
University of Pennsylvania, Philadelphia, Pennsylvania
University of California, Berkeley, California
University of California, Irvine, California
University of california, Los Angeles, California
University of Chicago/Argonne National Laboratory, Chicago, Illinois
University of Minnesota, Minneapolis, Minnesota
University of Michigan, Ann Arbor, Michigan
University of Tennessee, Knoxville, Tennessee
University of Texas Health Sciences Center, Houston, Texas
University of Washington, Seattle, Washington
University of Wisconsin, Madison, Wisconsin
Washington University, St. Louis, Missouri
West Los Angeles VA Medical Center, Wadsworth Division, UCLA, Los Angeles, California

a. Most centers in this list have both a cyclotron and PET. Some have PET only.

Table 2. Medical Cyclotrons**

Model	Proton Energy MeV	Deuteron Energy MeV	Beam Current μA
JSW 006[a]	---	6	60
JSW 126	12	6	60
JSW 1710	17	10	50
MC16F[b]	17	8.5	50
CGRSUM 325[c]	15	8	50
CGRSUM 370	17	10	50
CTI 112[d]	11	--	50
Oxford[e]	12	--	100

a. Japan Steel Works, Japan and USA
b. Scanditronix, Sweden and USA
c. CGR Sumitomo, Japan, France and USA
d. CTI, USA and Germany
e. Oxford, United Kingdom

** Current Contact Addresses for Cyclotron Manufacturers

(1) Computer Technology and Imaging Inc.
810 Innovation Drive
Knoxville, TN 37922
Alternate Contact
Siemens Medical Instruments
2000 Nuclear Drive
Des Plaines, IL 60018

(2) Japan Steel Works of America Inc.
Cyclotron Division
200 Ppark Avenue
New York, NY 10166

(3) Oxford Instruments Limited
Cyclotron Division
Eynsham
Oxford OX8 1TL
England

(4) Scanditronix Inc.
Nuclear Medicine Division
106 Western Avenue
P.O. Box 987
Essex, MA 01929

(5) Sumitomo Heavy Industries USA, Inc.
Nuclear Business Development Division
One World Trade Center
Suite 3669
New York, NY 10048

Table 3. Precursors for Synthesis

Carbon-11	^{11}CO	$^{11}CO_2$	$^{11}CN^-$	
Nitrogen-13	$^{13}N\text{-}N_2$	$^{13}NH_3$		
Oxygen-15	$^{15}O\text{-}O_2$	$C^{15}O$	$^{15}O\text{-}CO_2$	$H_2{}^{15}O$
Fluorine-18	$^{18}F\text{-}F_2$	$^{18}F^-$		

Table 4. Nuclear Reactions for Radionuclide Production

Carbon-11	$^{14}N(p,\alpha)^{11}C$	$^{11}B(p,n)^{11}C$	$^{10}B(d,n)^{11}C$
Nitrogen-13	$^{13}C(p,n)^{13}N$	$^{16}O(p,\alpha)^{13}N$	$^{12}C(d,n)^{13}N$
Oxygen-15	$^{15}N(p,n)^{15}O$		$^{14}N(d,n)^{15}O$
Fluorine-18	$^{18}O(p,n)^{18}F$		$^{20}Ne(d,\alpha)^{18}F$

Table 5. Some Theoretical Thick Target Yield Comparisons Versus Particle Energy*

Carbon-11 $^{14}N_g(p,\alpha)^{11}C$	Oxygen-15 $^{15}N_g(p,n)^{15}O$
16 MeV/10 MeV 172/62	16 MeV/10 MeV 156/60
Yield Ratio = 2.8	Yield Ratio = 2.6
Fluorine-18 $^{18}O(p,n)^{18}F(H_2{}^{18}O_\ell)$	
16 MeV/10 MeV 180/115	
Yield Ratio = 1.6	
Oxygen-15 $^{14}N_g(d,n)^{15}O$	Fluorine-18 $^{20}Ne_g(d,\alpha)^{18}F$
77 mCi/μA at 9 MeV	61 mCi/μA at 9 MeV

* Energies are on-target energies, not on target window energies. Thick target yields in mCi/μA are listed relative to high and low energies available from medical cyclotrons. Yield ratios are simply yield at 16 MeV over yield at 10 MeV.