A New Look at the Cyclotron for Making Short-Lived Isotopes (First Printed in 1966)

Michel M. Ter-Pogossian and Henry N. Wagner, Jr

This reprint of an article that first appeared in *Nucleonics* in 1966 provides a unique perspective of the introduction of the cyclotron into clinical medicine and medical research. The cyclotron offers a potentially powerful tool to biomedical centers. With this accelerator one can produce a variety of short-lived nuclides that are unavailable from other sources.

MOST RADIONUCLIDES used today in biomedical research and diagnostic medicine decay with half-lives that are long enough so that they can be transported from the place where they are prepared to the laboratories where they are used. With few exceptions the decay of these radionuclides does not impose stringent limits on the speed of delivery or the length of storage time before use.

But shorter-lived radionuclides that decay with a half-life less than ~10 hr cannot be shipped easily to distant laboratories without decaying substantially. This means that these nuclides must be prepared locally at the laboratory or hospital that plans to use them—a situation that requires considerably more effort on the part of the user. Nevertheless, the increasingly important place of short-lived nuclides in biomedicine[1,2] justifies the additional effort and has resulted in two approaches for preparing the radionuclides close to where they will be used. The first—and most widely used—is to make the isotopes in nuclide generators or "cows." The second—which will be discussed in this article—is to use cyclotrons.

Nuclide generators consist of a long-lived "parent" nuclide that produces a short-lived "daughter" nuclide as it decays. At intervals the user separates the daughter, usually by chemical means, and the parent is left to generate a fresh daughter.[3-7]

The first wide-spread application of a generator system in nuclear medicine was the Te^{132}-I^{132} system developed by Brookhaven National Laboratory in 1954. Other systems, such as the widely used Tc^{99m} generator, have since been devised at Brookhaven and elsewhere (two new cows for In^{113m} and Ba^{137m} are described on pages 57 and 60) to supply radionuclides with half-lives varying from a few minutes to several days. These systems are simple, relatively inexpensive and easily installed in even modest laboratories.

But unfortunately, few useful short-lived radionuclides can be prepared by this method. Therefore in most cases the optimum use of short-lived radionuclides in a biomedical environment requires their preparation by a reactor or accelerator. If we examine a chart of all radionuclides, we see that about half of them belong to the group of neutron-excess nuclides while the other half are neutron deficient. In general, neutron-excess nuclides are produced in reactors while neutron-deficient nuclides are produced in positive-ion accelerators such as the cyclotron. And because most of the short-lived radionuclides that are particularly useful in biology and medicine are of the neutron-

MICHEL M. TER-POGOSSIAN received his PhD in nuclear physics from Washington University in 1950. He joined the faculty of Washington University School of Medicine in 1950 where he holds a Professorship in Radiation Physics and in Physiology in addition to being Head of the Division of Radiation Physics and Nuclear Medicine.

HENRY WAGNER received his Doctor of Medicine from Johns Hopkins University School of Medicine in 1952. He joined the faculty of Johns Hopkins in 1959 where he holds Associate Professorships in Medicine, Radiology and Radiological Science in addition to being chief of Nuclear Medicine.

From Washington University School of Medicine, St. Louis, MO; and the Johns Hopkins Medical Institutions, Baltimore, MD.

Address reprint requests to Henry N. Wagner, Jr., MD, Professor of Medicine, Radiology and Radiation Health Sciences, The Johns Hopkins Medical Institutions, Room 2001, School of Hygiene and Public Health, 615 North Wolfe Street, Baltimore, MD 21205.

0001-2998/98/2803-0003$8.00/0

deficient type, the positive-ion accelerator holds out the potential of becoming a powerful tool for a well-equipped biomedical center.

At the present time there are only two cyclotrons in medical centers—one in London and the other in St. Louis. In the very near future a third one will be functioning at Massachusetts General Hospital in Boston. In addition, several medical centers in this country are contemplating installing cyclotrons in their laboratories. As these instruments become available in larger numbers there should be a rapid increase in both the fundamental and medical studies that are possible with short-lived radionuclides.

In addition, a cyclotron located in a biomedical center can be used to prepare longer-lived radionuclides such as Na^{24} and as a source of both fast and slow neutrons for radiobiological research, activation analysis and—perhaps in the future—radiation therapy.

WHY SHORT-LIVED TRACERS?

Why are these short-lived nuclides so useful in biology and medicine—perhaps even more so than their longer-lived counter-parts? Four distinct—but unrelated—advantages indicate the reason for their importance:

- When they are administered to a living organism, short-lived radionuclides result in less radiation dose.
- The radiation emitted by certain short-lived radionuclides makes them more desirable than longer-lived isotopes of the same nuclide.
- A certain number of nuclides that are useful in biomedical research have only short-lived radionuclides.
- And in certain cases a short-lived radionuclide can be prepared with a higher specific activity than its longer-lived isotope.

Clearly the first of these advantages is shared by all short-lived nuclides while the others are characteristic only of certain nuclides.

Any assessment of these advantages in biology and medicine requires a discussion of certain aspects that are specific to tracer methodology in living systems. The information elicited from a living organism by a radioactive tracer is always coded in the form of the radiation emitted by the radionuclide; therefore the amount of information extracted is limited by statistical fluctuations.

For example, at present the degree of spatial resolution one can achieve with external counting is low—approximately 1/25th of that with conventional radiographic procedures—primarily because of the statistical fluctuations in counting rate. These result from the limits imposed on the total amount of activity that can be used without radiation damage to the organism.

This situation improves considerably with the short-lived nuclides. Because of their short effective half-lives, more information (in the form of higher counting rates) is available with short-half-life nuclides for a given dose of radiation delivered to the system than with a longer-lived nuclide of the same element.

Of course the optimization of a given *in vivo* measurement with a radionuclide requires one to match the half-life of the nuclide to the phenomenon being studied. It is obvious that a radionuclide cannot be used to study a physiological process that is considerably longer than the half-life of the nuclide.

From the standpoint of radiation safety, the optimal physical half-life of a nuclide used to study a physiological phenomenon in a living organism is 0.69 times the elapsed time between administration of the labeled substance and measurement of the emitted radiation.[8] Although this time is less than a few hours in most medical applications, only seven of the nuclides now in use (Ga^{68}, F^{18}, I^{132}, Sr^{87m}, Tc^{99m}, Ba^{137m} and In^{113m}) have half-lives <12 hours. Consequently, there is a strong need for a wider choice of short-lived nuclides that can be given in large quantities without exposing the organism—and particularly the patient—to excessive radiation. Short-lived nuclides also have the advantage of letting one make repeated measurements in the same system because the rapidly disappearing activity does not interfere with subsequent measurements.

In addition to the rate of decay, the type of decay that a nuclide undergoes is an important factor in its usefulness in biology and medicine. Only x-rays, gamma rays, and positron annihilation radiation provide photons that can be detected outside a living organism. Beta particles, conversion electrons and low-energy photons are absorbed within the tissue where they contribute to the radiation dose but provide no useful information. Therefore in medicine and biology we need nuclides that are characterized by both optimum half-life and decay characteristics. Many short-lived radionuclides have

these desirable characteristics: for example, C^{11}, I^{123}, Fe^{52}, Cu^{61}, Cr^{49} and Hg^{199m}.

Many short-lived radionuclides are potentially very useful in biology and medicine not only because of their short half-lives or mode of decay, but also because there are no longer-lived radionuclides of the element. Examples are O^{15}, N^{13}, F^{18} and a number of others.

If we examine a comprehensive list of all radionuclides, we see that the most common half-life is ~1 hr; ~24% of the nuclides (~290) have a half-life of 1 hr-1 day, 20% (240) have a half-life of 1 day-1 year and 83 have a half-life >1 year. Of these nuclides a surprisingly small number have been used in biology and medicine. For example, a recent survey shows that 34 nuclides of 26 elements have been used at one time or another to study more than 70 body functions.[9] However, most of these investigations (>70% of the types of study) were carried out with only 9 nuclides of 6 elements—I^{131}, Cr^{51}, I^{125}, Tc^{99m}, I^{132}, Na^{22}, Kr^{85}, Hg^{197} and Hg^{203}. With the exception of Tc^{99m} these nuclides are far from ideal for use in man because they have neither the optimum decay characteristics nor half-lives suited for many of their uses. Thus under the circumstances it is quite apparent that short-lived radionuclides offer great promise as tracers in biology and medicine because of their half-lives, decay characteristics and chemical properties.

POSITIVE-ION ACCELERATORS

In addition to their advantages for producing neutron-deficient nuclides, positive-ion accelerators have two other features that make them ideal nuclide sources for medicine and biology. In the first place, the isotopes produced are carrier free—a great asset in studying trace constituents of the body which one wants to study without perturbing the physiological system. In the second place, positron-emitting nuclides are produced easily in positive-ion accelerators—giving one a higher degree of spatial resolution in measurements when they are used with a detection system designed for this purpose.

One should keep in mind that positive-ion accelerators can prepare any nuclide that can be obtained from a reactor if one uses the accelerators as neutron sources. In most instances, however, it is simpler and cheaper to prepare a neutron-generated radionuclide by irradiation in a reactor.

Table 1 lists a number of short-lived nuclides that can be prepared with a positive-ion accelerator and compares them with reactor-produced isotopes of the same element. The list also includes a number of accelerator-produced longer-lived nuclides that are potentially useful in biomedical research.

Positive ions can be accelerated by several types of instruments; the most common are cyclotrons and Van de Graaff generators. While the latter have been used in biomedical work, at the present time they appear to be vastly inferior to cyclotrons because the sizes needed to produce radionuclides are cumbersome and difficult to house. Other types of acclerators such as Cockroft-Walton accelerators and "Dynamitrons" which are capable of the energies needed for production purposes have not been developed.

ENERGY CONSIDERATIONS

The cross section of nuclear reactions resulting from positive-ion bombardment depends on the energy of the ions. These reactions can be broadly classified into two categories: (1) exoergic (or exothermic) reactions and (2) endoergic or (endothermic) reactions. In exoergic reactions energy is released subsequent to the interaction of the positive ion with the nucleus. Consequently, these reactions can be initiated even by "zero-energy" positive ions. Exoergic reactions with positively charged particles can take place only if the bombarding particle carries sufficient kinetic energy to overcome the electrostatic repulsion (Coulomb barrier) of the positively charged nucleus. This barrier increases with the charge on the nucleus and the charge of the bombarding particle. The energy required to overcome the Coulomb barrier, however, does not intervene in the nuclear reaction.

Endoergic reactions, on the other hand, absorb energy and can take place only if the impinging particle carries a sufficient "threshold energy" below which the reaction will not take place. The amount of energy either absorbed or released in a nuclear reaction is expressed as the Q value for the reaction. Q is negative for endoergic reactions and positive for exoergic reactions.[10] Table 1 gives the Q values for the nuclear reactions listed.

In general, the cross section of a nuclear reaction resulting from positive-ion bombardment increases with the energy of the particle above the threshold value, reaches a maximum value and then decreases as Fig. 1 shows. The rise in cross section

Table 1. Short-Lived Isotopes From Accelerators and Reactors

Accelerator-Produced Radionuclides							Reactor-Produced Radionuclides			
Atomic Number	Element	Nuclide	Half-life	Decay and Principal Radiations Emitted (Mev)	Method of Generation	Q (Mev)	Nuclide	Half-life	Decay and Principal Radiations Emitted (Mev)	Method of Generation
4	Be	Be^{7}	53 d	EC; γ0.48	$Li^{7}(p, n)Be^{7}$	−1.64				
6	C	C^{11}	20.5 min	β^{+}0.96	$B^{10}(d, n)C^{11}$	6.47	C^{14}	5,730 y	β^{-}0.156	$N^{14}(n, p)C^{14}$
7	N	N^{13}	9.96 min	β^{+}1.19	$B^{10}(\alpha, n)N^{13}$	1.06				
8	O	O^{15}	124 sec	β^{+}1.74	$N^{14}(d, n)O^{15}$	5.06				
9	F	F^{18}	110 min	β^{+}(97%) 0.649; EC (3%)	$O^{16}(\alpha, pn)F^{18}$	−18.6	F^{18}	110 min	β^{+}0.649	$Li^{6}(n, \alpha)H^{3}$ followed by $O^{16}(H^{3}, n)F^{18}$
17	Cl	Cl^{34m}	32 min	β^{+}2.5, 1.3; γ2.04, . .	$P^{31}(\alpha, n)Cl^{34m}$	−5.57	Cl^{36}	3×10^{5}y	β^{-}(98%)0.71, EC (2%)	$Cl^{35}(n, \gamma)Cl^{36}$
17	Cl						Cl^{38}	37.3 min	β^{-}4.8, 1.1, 2.8; γ2.2, 1.6	$Cl^{37}(n, \gamma)Cl^{38}$
19	K	K^{38}	7.7 min	β^{+}2.7; γ2.2	$Cl^{35}(\alpha, n)K^{38}$	−5.87				
19	K	K^{42}	12.4 hr	β^{-}3.53, 2.01; γ1.52, . .	$K^{41}(d, p)K^{42}$	5.30	K^{42}	12.4 hr	β^{-}3.53, 2.01; γ1.52, . .	$K^{41}(n, \gamma)K^{42}$
20	Ca	Ca^{47}	4.7 d	β^{-}1.98, 0.67; γ1.31, . .	$Ca^{46}(d, p)Ca^{47}$	5.08	Ca^{45}	165 d	β^{-}0.25	$Ca^{44}(n, \gamma)Ca^{45}$ $Sc^{45}(n, p)Ca^{45}$
26	Fe	Fe^{52}	8.3 hr	β^{+}(57%)0.80, (2.63); EC (43%) γ0.17	$Cr^{50}(\alpha, 2n)Fe^{52}$	−15.65	Fe^{55}	2.7 y	EC	$Fe^{54}(n, \gamma)Fe^{55}$
26	Fe						Fe^{59}	45 d	β^{-}0.46, 0.27, 1.56; γ1.29, 1.10, 0.19, . .	$Fe^{58}(n,\gamma)Fe^{59}$
30	Zn	Zn^{63}	38 min	β^{+}(93%)2.35; EC (7%); γ0.67, 0.97, 0.81-2.9	$Cu^{63}(d, 2n)Zn^{63}$	−6.37	Zn^{65}	245 d	EC (97.5%); β^{+}(2.5%) 0.33; γ1.12	$Zn^{64}(n, \gamma)Zn^{65}$
53	I	I^{123}	13 hr	EC; γ0.159, . .	$Te^{123}(p,n)I^{123}$		I^{128}	25.0 min	β^{-}(94%)2.12, 1.67, . . ; EC (6%); γ0.44, 0.53	$I^{127}(n, \gamma)I^{128}$
53	I	I^{124}	4.2 d	EC (70%); β^{+}(30%)1.55, 2.15, . . ; γ0.60, 1.7, 0.65-2.9	$Sb^{121}(\alpha, n)I^{124}$	−7.91	I^{130}	12.5 hr	β^{-}1.02, 0.60; γ0.66, 0.53, 0.74, 1.15, 0.41	$I^{129}(n, \gamma)I^{130}$
53	I	I^{126}	13.2 d	EC (58%); β^{-}(40%)0.38; β^{+}(2%)1.13, . . −1.25; γ0.39, 0.67, 0.48-141	$Sb^{123}(\alpha, n)I^{126}$	−6.92	I^{131}	8.05 d	β^{-}0.61, 0.25-0.81; γ0.36, 0.0800-0.72	Fission

results mainly from the increased facility with which the charged particle penetrates the Coulomb barrier, while the decrease results chiefly from competition with other nuclear reactions that may arise at higher energies.[10] The excitation curve can also exhibit resonance peaks.

When one prepares a radioactive isotope by bombarding a target material with accelerated positive ions, the yield of the reaction—expressed, for example, as activity produced per number of positive ions impinging upon the target—can be predicted from the cross section of the reaction. If the target material is infinitely thin and if the particles lose very little energy while they are passing through the target, the cross section remains constant, and the curve for yield as a function of energy follows the same pattern as the excitation curve. If, on the other hand, the target is thick—as is usually the case for radionuclide preparation—the particles lose their energy in the

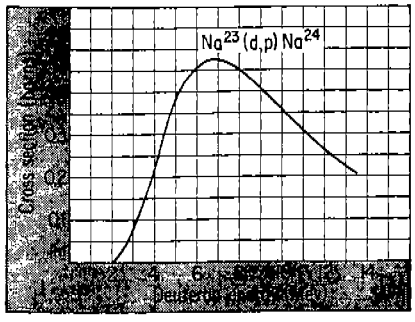

Fig 1. Cross-section for reaction resulting from positive-ion bombardment—shown at left for Na^{23} (*d,p*) Na^{24} reaction—increases with particle energy above threshold value, reaches maximum and then decreases.[10]

target where they are eventually stopped, and the curve shows an initial fast rise (Fig 2) followed by a much slower rise, (Fig 3).[11]

The selection of the energy rating for a positive-ion accelerator is determined by the Q-value one needs to initiate the particular nuclear reactions. One must keep in mind that the energy of the accelerated positive ions must exceed the Q value of the reaction by the energy needed to overcome the Coulomb barrier of the nucleus. Also, if an external beam of charged particles is used to prepare the isotope, the energy of the particles must exceed the Q value of the reactions by the energy lost by the particles as they traverse the window separating the evacuated cyclotron chamber from the target material. Such an energy drop depends on the energy of the particles and is of the order of 1 Mev per 0.05 mm of aluminum for 10-Mev deuterons.

Because of these considerations and because the

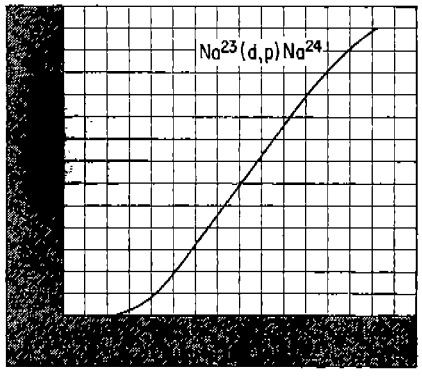

Fig 2. Yield of Na^{24} prepared by Na^{23} (*d,p*) Na^{24} reaction on thick target as function of deuteron kinetic energy is shown above.[10]

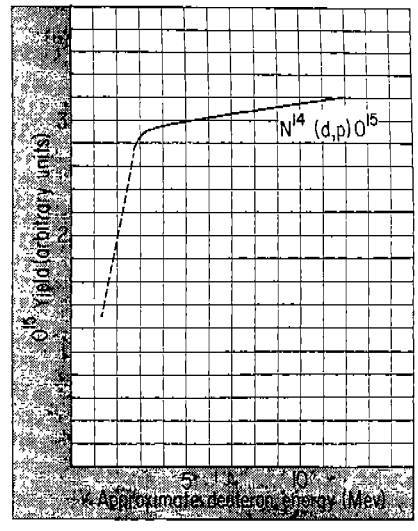

Fig 3. Yield of production of O^{15} by N^{14} (*d,n*) O^{15} reaction as function of deuteron kinetic energy is shown at right.[11]

yield of a nuclear reaction for a thick target increases with the energy of the accelerated particles, it is usually desirable when preparing a radioactive isotope to exceed the Q value of the nuclear reaction by several Mev. However, for certain radioisotopes it may be preferable not to exceed a given energy for the bombarding particles to prevent the formation of undesirable impurities that may be generated at higher energies. This is the case when one prepares O^{15} by deuteron irradiation of nitrogen. In this exoergic reaction one should maintain the energy of the deuterons close to ~3 Mev. Indeed, for this reaction the yield does not increase substantially with energies above 3 Mev, and the use of higher-energy deuterons increases the amount of undesirable C^{11} contamination.[11]

Any radionuclide is potentially useful for biomedical applications. Therefore, it appears that specifications for a cyclotron designed to prepare biologically useful radioactive tracers should call for a high-beam intensity, high-energy machine capable of initiating any nuclear reaction resulting in a useful nuclide. A high-energy machine of this kind would also have the advantage over lower-energy accelerators of producing higher radioisotope yields. If lower energy ions are needed from a high-energy machine, the energy of the ions can always be reduced by absorption. Accelerators capable of generating positive ions with an energy of ~10 Mev/nucleon can produce, for all practical purposes, any desired nuclide; therefore, much

higher-energy bombarding particles are unnecessary for isotope production.

COST CONSIDERATIONS

The discussion of energy considerations does not take into account the cost limitations imposed on (1) the space needed, (2) the construction and (3) the operation (including personnel) of a large accelerator. Unfortunately, the size of a cyclotron, its cost, the cost of the building that houses it and the shielding it needs, the cost of operating and maintaining the machine, the salaries of the personnel to operate it and the general difficulties encountered in its operation increase sharply with the energy capabilities of the machine.

A gross rule of thumb is that the cost of the cyclotron is a power function with an exponent between 2 and 3 of the energy of the particles accelerated; on the other hand, its housing, the personnel required for its operation and the maintenance and operating cost are linear functions of the energy.

At times a compromise must be made between a cyclotron ideally designed for biomedical research (~20 Mev deuterons) and a smaller, cheaper and simpler machine, which—while unsuitable for initiating certain nuclear reactions—is adequate for generating most useful isotopes. In fact, such compromise between the energy capabilities of a cyclotron and its cost is only moderately restrictive in biomedical research for the following reason.

In most instances the isotope one wants can be prepared by several nuclear reactions on different nuclides, each with a different Q value. The energy capabilities of a cyclotron for accelerating positive ions are given by the formula $E = B^2Ro^2e^2/2m$ in which E is the kinetic energy of the accelerated ion, B is the flux density of the magnetic field, Ro is the radius of the outer-most orbit, m is the mass of the particle and e is the elementary charge. The required oscillator frequency (f) is $fo = Be/2\pi m$. Thus the energy capabilities of the cyclotron are limited for a given ion by the flux density of the magnetic field and by the maximum size of the pole pieces of the magnet; moreover, the energy of the positive ion accelerated is proportional to e^2/m.

Table 2 shows the approximate energies of various ions accelerated in a cyclotron. With a lower-energy cyclotron one can prepare a radioisotope by selecting a suitable bombarding particle even though the nuclide may be impossible to

Table 2. Cyclotron Parameters for Fixed Outer Radius

		Fixed Frequency E – Be		Fixed Magnetic Field E – e^2/m*	
	Ion	B	E	f_0	E
(Proton)	H^1	1	1	1	1
(Deuteron)	H^2	2	2	1/2	1/2
(Triton)	H^3	3	3	1/3	1/3
(Helium nucleus)	He^3	3/2	3	2/3	4/3
(Alpha particle)	He^4	2	4	1/2	1

*In these calculations m is replaced in the cyclotron equations by the mass number A.

generate with the lower e^2/m projectile. For example Fe^{52} can be prepared with a large cyclotron by the α, $2n$ reaction on Cr^{50} with a Q value of -15.6 Mev or by the He^3, $3n$ reaction on Cr^{52} which gives a good yield with a lower-energy machine. Of course, in choosing a particular nuclear reaction for preparing an isotope one must also consider the cross section of the reaction, the isotopic abundance of the target material and the possible generation of radioactive impurities.

To summarize, larger cyclotrons are preferable to smaller ones for biomedical research because of the broader spectrum nuclear reactions that are possible with them and because of the greater yields that are achieved with higher energies. However, the selection of a smaller unit does not result in too stringent compromises because of the wide choice of nuclear reactions leading to production of a particular isotope and because the amounts of activity required in tracer work in general are modest. An examination of the Q values in Table 1 shows that a cyclotron capable of accelerating deuterons to an energy of ~8 Mev, protons to an energy of 16 Mev, alpha particles to an energy of 16 Mev and He^3 nuclei to an energy of ~26 Mev is a good source of most of the isotopes listed. A unit with this capability is relatively inexpensive, and its installation and operation in a hospital are uncomplicated.

The usefulness of He^3 as a projectile for various nuclear reactions deserves to be emphasized. The e^2/m ratio of 4/3 for this particle makes it particularly desirable because of the high energy that can be imparted to the particle even in a modest-size cyclotron; and a great number of nuclear reactions that use He^3—such as He^3, $3n$; He^3, $2n$; and H^3, p—lead to the generation of a number of radioactive isotopes that are useful in biomedical research.

Despite its advantages, the acceleration of He^3

ions does impose certain constrictions on the cyclotron. In the first place the high cost of He^3 makes a recovery system in the cyclotron for this gas mandatory; however, such a recovery system is relatively inexpensive and functions well. In the second place, adequate focusing of He^3 is easier in an azimuthally focused rather than in a uniform-field machine.

The choice between the more desirable, but costly and complex, high-energy machine, and the more limited, but cheap, lower-energy machine is illustrated by the two cyclotrons that are now installed in medical centers. These are the Medical Research Council Cyclotron located at the Hammersmith Hospital (capable of accelerating deuterons to 15 Mev) in London[12,13] and the Washington University Medical Cyclotron (6-8-Mev deuterons) located in St. Louis, Fig 4, 5, Table 3. The cost items for the Washington University Medical Cyclotron are:

Cost of unit	~$200,000
Room and shielding	~$ 60,000
Yearly operation and maintenance costs (for heavy operation)	~$ 15,000
Required personnel	2 operators

Housing and Shielding

Because a cyclotron produces neutrons and electromagnetic radiation during operation, the areas

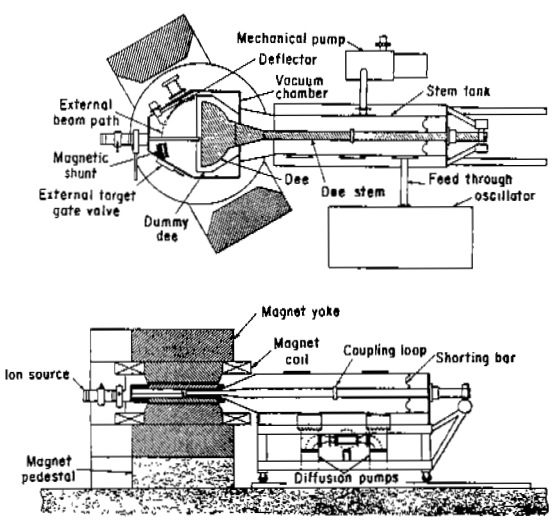

Fig 4. Line diagrams of Washington University Medical School cyclotron (Reproduced by courtesy of Am J Roentgenol Rad Therapy & Nuc Med).

Fig 5. Rear aspect of Washington University Medical School cyclotron (Reproduced by courtesy of Am J Roentgenol, Rad, Therapy & Nuc Med).

around it must be shielded against these radiations. The Washington University cyclotron is housed in a room 14 ft wide and 24 ft long. The room, which is 9 ft high, is sunk underground to a depth of 5 ft 4 in. Additional shielding for this installation is 3 ft of concrete. This arrangement was dictated by the space available and by the undesirability of disturbing the footings of the Barnard Hospital building in which the unit is housed. A maze shields the access to the room. The adequacy of the shielding was determined for both gamma ray and neutron hazards created by bombarding copper and beryllium targets with deuterons. The maximum measured radiation fields in normally occupied areas are <0.1 mrem/hr/μa beam current on the target with a beryllium target (the radiation field is much lower with a copper target). The maximum reading obtained within 1 ft of the wall is 0.7 mrem/hr/μa.

During cyclotron operation the air in the room is activated, mostly by O^{15} formation. To prevent diffusion of this activity, the room is vented only when the machine is turned off. Under these circumstances no radiation hazard exists because of room ventilation.

Another type of commercially manufactured small cyclotron is shown in Fig 6. This instrument, which is manufactured by the Cyclotron Corporation, is of the azimuthally varying field type and is more compact than a uniform-field unit with the same output. The specifications for the cyclotron are given in Table 3.

C^{11} AND O^{15} FROM ACCELERATOR

We shall discuss only two cyclotron-produced nuclides, C^{11} and O^{15}, which are of such importance in biology that their availability in a medical center gives the most promise.

Table 3. Specifications for Two Medical Cyclotrons

Type: Fixed frequency—Uniform magnetic field cyclotron.
Over-all Dimensions: 6 × 9 × 16 ft
Housing for Accelerator and Power Supplies: 24 × 14 × 9-ft shielded room
Weight: Cyclotron and oscillator: 56,300 lb
Power supplies: 9,800 lb
Control console: 1,500 lb
Utilities: Power: 150 kva, 440 v 3 phase 60 cps
Cooling water: 230 liters/min
Magnet: Pole diameter: 36 in.
Pole tip diameter: 33 in.
Exit radius: 14 in.
Mean field at exit radius: 14 kilogauss
Maximum current in conductor: 650 amp
d-c power required: 40 kw
Current regulation accuracy: $1/10^5$
Oscillator System: Operating frequencies: 21.3 Mc/sec (protons)
10.65 Mc/sec (deuterons)
14.2 Mc/sec (He^3)
Number of dees: 1
Dee to ground peak voltage: 50 kv
Available d-c power at rectifier: 50 kw
Deflector maximum voltage: 75 kv
Ion Source: Type: Hooded—hot cathode
Maximum filament current: 200 amp
Filament power supply maximum voltage: 6 volts
Performance: Deuteron energy: 6-8 Mev
(The cyclotron design allows acceleration of deuterons up to 8 Mev, however, the machine is presently used at 6 Mev)

Measured Values:	Deuteron internal beam: ~200 μa
	Deuteron external beam stable operation: 40 μa maximum
	measured: 60 μa
Potential Performance	Proton energy: 12-16 Mev
	Helium-3 ion energy: 16-21 Mev
	Helium-4 ion energy: 12-16 Mev
	Beam size at exit port: 2 mm × 25 mm (approx.)

Type: Isochronous, fixed frequency, azimuthally varying field-cyclotron.
Over-all Dimensions: 7 × 7 × 7 ft
Housing for Accelerator and Power Supplies: 15 × 15 ft shielded room
Weight: Cyclotron: 30,000 lb
Power supplies: 4,000 lb
Controls: 2,000 lb
Utilities: Power: 150 kva, 480 v, 3 phase 50 or 60 cps 25 kva, 115 v, 1 phase
Water: 50 gallons/min
Magnet: Pole tip diameter: 30 in.
Average field: 16.5 kilogauss
d-c power required: 40 kw
Current regulation accuracy: $1/10^4$
Oscillator System: Operating frequencies: 25 Mc/sec for protons
12.5 Mc/sec for deuterons
16.7 Mc/sec for He^2 particles
Number of dees: 2 (120 deg)
Dee to ground peak potential: 30 kv
Dee voltage regulation: $1/10^2$
Dee frequency regulation: $1/10^5$
Ion Source: Penning ion gage (PIG) source.
Performance:

Particle:	**Proton**	**Deuteron**	**He^3**	**Fast neutron[1]** (n/cm²/sec)	**Thermal neutron[2]** (n/cm²/sec)
Energy:	15 Mev	7.5 Mev	20 Mev		
Resolution:	75 kev	38 kev	100 kev		
Extracted Beam Current:	50 μa	50 μa	50 μa	2×10^{12}	5×10^9

[1]$Be^9(d,n)$ B^{10} thick target [2]With paraffin moderator
Beam size at exit port: 0.5 in. diameter
0.05 radian divergence

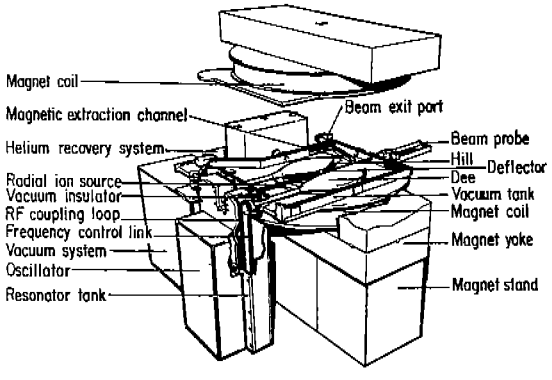

Fig 6. Azimuthally varying field (AVF) designed cyclotron by Cyclotron Corp.

Using C^{11}

Although the most important radioactive tracer in biological research is probably reactor-produced C^{14}, this nuclide suffers from three deficiencies: (1) its long half-life of over 5,000 years precludes its use in human *in vivo* tracer work for compounds with a long biological half-life, (2) its long half-life prevents one from making repeated experiments on the same system because of rising background and (3) it decays with the emission of soft beta rays which for all practical purposes cannot be detected in *in vivo* experiments. Because of these drawbacks, C^{14} has never been widely used in nuclear medicine.

C^{11}, on the other hand, does not have these limitations. Its half-life is only 20.4 min,[15] and it decays by emitting ~100% 0.972-Mev positrons with emission of annihilation radiation which can be detected easily at great distances from the site of emission either by a single counter or by two counters in coincidence allowing precise spatial localization. Electron capture is ~0.19%.[16] The main disadvantage of C^{11} as a tracer is its short half-life which limits its use to compounds that can be rapidly labeled and to experiments in which the label is followed for only a short period of time. In certain cases the first drawback can be circumvented by using fast labeling techniques such as fast synthesis, exchange reactions or recoil labeling.[17] However, the second defect presents an insurmountable barrier to the use of C^{11} in a number of studies. Nevertheless, the importance of carbon in biology is so great that there seems to be little doubt C^{11} can be used in many studies that have been impossible before.

C^{11} was used as a radioactive tracer in biological experiments even before the discovery of C^{14}. A large number of organic compounds, including acetic acid, lactic acid, succinic and fumaric acids were studied after labeling with C^{11}.[18] In spite of its short half-life, C^{11} has also been used as a label in biosynthesis.[19] More recently Stenström has described a method for labeling inulin with C^{11} by recoil.[20]

C^{11} has been used extensively in the form of carbon monoxide and carbon dioxide in human experimentation. The first application of the nuclide was in a medical study in which it was used for labeling carbon monoxide.[21,22] Carbon-labeled carbon monoxide provides an excellent and simple way to label red blood cells for localizing blood pools by external scanning (for the diagnosis of pericardial effusions or for localization of placenta) or for repeated blood-volume determinations which are facilitated by the short half-life of the radioactive label. C^{11}-labeled carbon monoxide and carbon dioxide have also been used to study pulmonary function.[23]

C^{11} is prepared in the B^{11} (d,n) C^{11} reaction[24] by bombarding boron oxide (B_2O_3) with cyclotron-accelerated deuterons.[25] The C^{11} escapes the solid target in the form of carbon monoxide and carbon dioxide and can be extracted and used either by sweeping these gases by a continuous flow of inert gas as is done at Hammersmith in England or by collecting the gas from the irradiated chamber after irradiation as is done in the Washington University cyclotron (Fig 7). If one wants carbon monoxide, the carbon dioxide can be removed from the mixture by passing the radioactive gases over soda lime. On the other hand, if carbon dioxide is more useful, the carbon monoxide can be oxidized in the mixture of the two gases by oxidation in the presence of a catalyzer. The cross section of the nuclear reaction leading to C^{11} generation lets one prepare very high activities of C^{11} even with modest cyclotron beam currents.

Using O^{15}

O^{15} is the longest-lived radioactive isotope of oxygen, decaying with a half-life of 122 sec.[15] It decays by emitting 1.726-Mev positrons.[15] It might appear that its short-half-life would preclude its use in biological research; however, O^{15} is a very valuable tracer in biology because of the combination of two factors: (1) oxidation is the fundamental phenomenon in the life of higher organisms, and probably the most reliable index of the metabolism of a tissue is its rate of oxidation. (2) Metabolic oxidation is a process which in most of its phases is comparable in time scale to the half-life of oxygen; therefore O^{15} can indeed be used to study many phases of metabolism. Thus the combination of the need for a radioactive tracer of oxygen and the fact

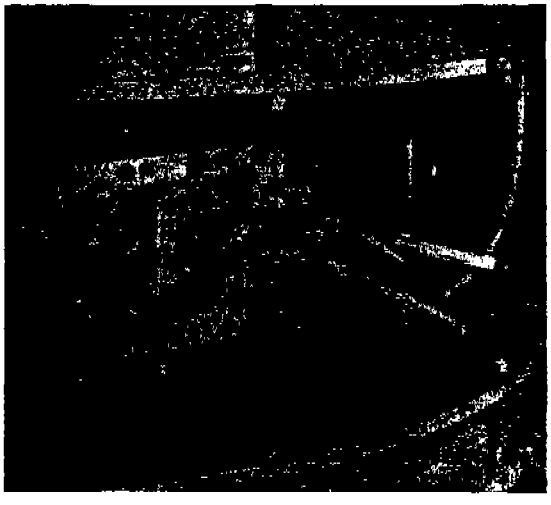

Fig 7. Irradiation chamber for preparing C^{11}-labeled carbon monoxide and carbon dioxide by deuteron bombardment of boron oxide. Radioactive gases are withdrawn by one of two syringes shown.

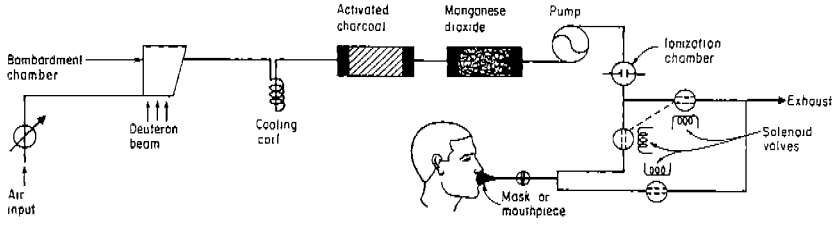

Fig 8. Simplified block diagram of system used in conjunction with Washington University Medical School cyclotron for preparation, purification and utilization of O^{15} used in medical studies.

that most phenomena studied that way are short in duration has made O^{15} a useful and particularly attractive tracer in biological and medical studies.

O^{15} has been used in biology and medicine as a tracer for oxygen,[26-31] carbon monoxide,[28,32] carbon dioxide[28,33,34] and water.[35] In general terms, oxygen has been extensively used in medical and biological studies in the metabolism of oxygen, in pulmonary function and in the determination of the metabolism in normal structures and in neoplasms.[36,37] There is not much doubt that this isotope will become extremely important in nuclear medicine when a greater number of cyclotrons become available.

O^{15} is prepared by bombarding nitrogen with deuterons by the N^{14} (d,n) O^{15} reaction.[24] This reaction is exoergic, and the kinetic energy of the deuterons needs only to exceed the Coulomb repulsion of oxygen for the reaction to take place. Dyson and his group[11] have shown that the optimum energy for O^{15} production is 3 Mev; above this energy the yield does not increase appreciably, while at 2 Mev this yield is appreciably lower (Fig 3).

The target material used is air at NTP circulating continuously in the cyclotron beam (Fig 8) (or it may be nitrogen containing a small amount of O_2 carrier). The air is bombarded in a chamber that is sufficiently deep to absorb the energy of the deuterons. In this system the O^{15} is obtained mixed with normal air. The intense ionization produced by the cyclotron beam in air and the recoil energy of the activated oxygen atoms results in the formation of a number of chemical impurities—the most important ones being ozone and nitrogen oxides. These contaminants can be removed by filtering the activated air with activated charcoal and manganese dioxide. The radioactive impurities produced by this method are not generated in sufficient amounts to interfere with most experiments.

REFERENCES

1. Newbery GR: Br J Radiol 32:633-641, 1959
2. Ter-Pogossian MM: "Progress in Atomic Medicine," Vol. 1, JH Lawrence, ed. Grune & Stratton, New York, London, 1956
3. Harper PV, et al: Optimization of a scanning method using Tc^{99m}. Nucleonics 22:50-54, 1964
4. Gleason, GI: Intern J Appl. Radiation & Isotopes 8:90, 1960
5. Greene MW, Tucker, WD: Intern J Appl. Radiation & Isotopes 12:62, 1961
6. Yano Y, Anger HO: J Nuclear Med 5:484-487, 1964
7. Myers WG, Olejar M: J Nuclear Med 4:202, 1963
8. Wagner HN Jr, Emmons H: Characteristics of an ideal radiopharmaceutical in radioactive pharmaceuticals (U.S. Atomic Energy Commission, Division of Technical Information)
9. Silver S: Uses of radioisotopes in medicine. Nucleonics 23:106, 1965
10. Whitehouse WJ, Putman JL: Radioactive Isotopes. Oxford: Clarendon Press, 1953
11. Dyson NA, et al: Proceedings of the 2nd U.N. Intern. Conf. on the Peaceful Uses of Atomic Energy. UN, Geneva, September, 1958. Pergamon Press, London, New York, Paris, 1959
12. Howard FT: Cyclotrons and high energy accelerators, ORNL-2644, 1958
13. Gallop JW, et al: Proceedings of the Inst. Elec. Engrs. Part B, civ. 451, 1957
14. Ter-Pogossian MM: Am J Roentgenol. Radium Therapy and Nuclear Med. 96:737-743, 1966
15. Nuclear Data Tables: Part 4 US Atomic Energy Commission, Government Printing Office, Washington, DC, 1960
16. Radiological Health Handbook: US Dept of Health, Education and Welfare, Government Printing Office, Washington, DC, 1960
17. Wolf AP: U.M.E.S.C.O./NS/RIC/202
18. Buchanan JM, Hastings AB: Physiol Revs 26:120, 1946
19. Ruben S, Hassid WZ, Kamen MD: J Am Chem Soc 61:661, 1939
20. Stenstrom T: Scientific Report No. 5, AF EOAR Contract #AF61 (052)-740, 1965
21. Tobias CA, et al: Am J Physiol 145:253-263, 1945
22. Lawrence JH, Tobias CA: Air Surg Bull 2:452, 1945
23. Newbery GR: Brit J Radiol 32:633-641, 1959
24. Nuclear Data: Circular No. 499, National Bureau of Standards, Government Printing Office, Washington, DC, 1950

25. Buckingham PD, Forse GR: Intern J Appl. Radiation and Isotopes 14:439-445, 1963

26. Dyson NA, Sinclair JO, West JB: J Physiol 152:325-336, 1960

27. Dyson NA et al: Br Med J 1:231-238, 1960

28. Dollery CT, West JB: Circulation Research 8:765-771, 1960

29. Dollery CT, West JB: Nature 189:1121, 1960

30. Spratt JS Jr, et al: Forum 12:7-9, 1961

31. Spratt JS Jr, et al: Surgery 50:941-946, 1961

32. Dollery CT, Dyson NA, Sinclair JD: Physiol. 15:411-417, 1960

33. West JB, Dollery CT: J Appl Phys. 15:405-411, 1960

34. West JB, Dollery CT: J Appl Physiol. 17:9-13, 1962

35. West JB, Dollery CT: Nature 189:588, 1961

36. Ter-Pogossian M, Powers WE: Radioisotopes in scientific research. Vol 3. In: Proc 1st U.M.E.S.C.O. Intern Conf. (Paris, 1957). Pergamon Press, London, New York, Paris, 1958

37. Ter-Pogossian M, et al: Use of oxygen-15 for the determination of the metabolism of normal tissues (to be published)