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CYCLOTRONS AND POSITRON EMITTING RADIOPHARMACEUTICALS

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INTRODUCTION

Positron Emission Tomography is at the present time in a growth phase with an increasing number of clinical facilities showing interest in the use of PET in routine practice. The consequences of this fact, not only for the technology of PET but also for cyclotron application and radiopharmaceutical production, necessitate a review of what is possible given today's state-of-the-art.

We are now approaching the end of the first decade in which we witnessed the maturing of the three essential components of the PET methodology: radiotracers, positron emission tomographs and tracer kinetic models. As a result, from 1976 to the present, the number of centers acquiring the instrumentation and core team of scientists applying PET to problems in the health sciences has grown exponentially. In the U.S. in 1979, the National Institutes of Health funded the establishment of several regional centers and embarked on a large PET program of its own. All of this was based on the assumption that PET would be able to test a number of important scientific hypotheses in the living human body, that it will provide the means of quantitatively describing disease as well as normal function at the molecular level, and that its use would provide guidance in disease therapy. That PET is already making a contribution in choosing the treatment of certain disease (for example epilepsy, stroke, heart disease) has been recently recognized by the establishment

of clinical centers. However, the success of PET as a scientific tool requires not only that investigators proceed beyond the instant gratification provided by a color image but address more difficult issues such as instrument limitations and biochemical and physiological significance of PET measurements. It follows that they use PET to address significant scientific questions.

Basic biomedical research with PET requires a broadly based research team and flexibility in radiotracer production as the demands and interests of the research group changes. This may not be the case in a purely clinical facility where the spectrum of probes is more restricted and depends almost entirely on what are proven compounds with general utility. So, for example, a clinical facility based on using the labeled oxygen moieties O_2, H_2O, CO, and CO_2, labeled deoxyglucose and perhaps a labeled neuroleptic could operate at a limited level with a cyclotron delivering its particles to "black boxes" (a device which is connected directly to the cyclotron target and which can purify a labeled gas or prepare a labeled compound by automated synthesis), and then delivering the needed labeled tracer to a gas bag, or into a gas delivery line or into a multi-injection vial. Such a facility could be operated by technical personnel. It should also be clear under such conditions that the user would be dependent on the manufacturer as a source of "black boxes" for any new useful tracer that might appear. Sufficient flexibility to carry out new synthesis and development in an independent manner bespeaks of a much larger cadre of professionals with a suitable infrastructure.

It is the purpose of this paper to focus on aspects of cyclotron and labeled tracer preparation in light of what is possible today. The references in this paper are not intended to be comprehensive. However, source material and further literature references can be found in these papers. Two books (1,2) have recently been published on positron emission tomography which contain a wealth of material on all aspects of the subject including the subjects addressed in this paper.

Cyclotrons and Radionuclide Production

The cyclotrons currently available are listed in Table I. At the present moment two more manufacturers (Meditron, The Eindhoven, The Netherlands and Shimadzu Co., Japan) are considering supplying machines of the type listed in Table I, however, no concrete plans have as yet been announced, nor is their technical data available.

An elementary description of the technical aspects of cyclotrons is available (3).

Table I
Small Cyclotrons

	Protons, MeV	Deuterons, MeV	Current, μA
JSWBC168	16	8	50
JSWBC1710	17	10	50
MC 16F	17	8.5	50
CGR MeV SUM 325	15	8	50
CGR MeV SUM 370	17	10	50
CTI	11	None	50

JSW - Japan Steel Works, Japan
MC - Scanditronix, Sweden
CGR - CGR Sumitomo, France and Japan
CTI - Computer Technology and Imaging, USA

Two choices can be made with regard to machine type, two particle, i.e. protons and deuterons and one particle proton only. Parenthetically it is worth noting that the earliest machines used full time for medical purposes, those at Hammersmith Hospital, London, Massachusetts General Hospital, Boston, and Washington University, St. Louis were either deuteron only machines or in the case of the Hammersmith machine, deuterons and alpha particles. While a great deal of pioneering work was done with these machines, it became evident that flexibility in research and application required a two particle machine, i.e. protons and deuterons. There are approximately 25 machines of the type listed in Table I in use today. A current listing of cyclotron PET facilities can be found in reference (4). At this writing, the single particle 11 MeV proton only machine has as yet to be installed and tested for general efficacy in a biomedical program. A proton only machine requires the use of enriched stable isotopes for the production of nitrogen-13, oxygen-15 and fluorine-18.

Table II
Positron Emitter Production Reactions Using a Small Cyclotron (p,d)

	Proton Reactions		Deuteron Reactions
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	$^{18}O(p,n)^{18}F$		$^{20}Ne(d,\alpha)^{18}F$

The nuclear reactions which are used to produce the four positron emitters (^{11}C, ^{13}N, ^{15}O, ^{18}F) accounting for over 95% of research with PET today, are listed in Table II. Other useful positron emitters such as gallium-68, bromine-75, strontium-82, and iodine-122 are not covered here since they cannot be effectively prepared using machines of the type listed in Table I.

Let us consider what production levels are possible using these small machines. In order that yield estimates can be made, accurate excitation functions needed to be determined experimentally as a first step in deciding whether or not a particular nuclear reaction were of practical use. Functions for carbon-11 (5) via $^{14}N(p,\alpha)^{11}C$, oxygen-15 (6,7,8) via $^{14}N(d,n)^{15}O$, and $^{15}N(p,n)^{15}O$ and fluorine-18 (9,10,11) via $^{18}O(p,n)^{18}F$ and $^{20}Ne(d,a)^{18}F$ have been published. These references (5-11) give tables or graphs giving thick target saturation yields as a function of particle energy on target. Data from these papers is presented in Tables III-VIII in condensed form and relative only to machines listed in Table I in order to provide a sampling of what practical yields are obtainable, given the energies available. Clearly a "practical yield" is arbitrarily chosen. The choice is based on the minimum time of beam-on-target which provides sufficient radioisotope to effect a synthesis of a needed labeled tracer. Because of its short half-life, carbon-11 production can approach the saturation yield if one bombards for longer than one hour. Twenty microamps was chosen as the beam current since in our experience not a great deal is to be gained by higher beam currents due to the gas density reduction problem (vide infra) which is exacerbated at higher beam currents. It is of course possible with altered target design and a change in beam cross section etc. to go to higher beam currents. Such targets remain to be described in the literature. However,

considering what is known and available today, currents between 15 and 30 μA depending on target type are optimal for production runs. A word of caution must be introduced with regard to the last column of the tables. The assumption is made that 100% of the beam hits the target and negligible wall loss occurs due to beam spread. Thus the data should only be used as a guideline since it ignores the aforestated and other possible perturbations. Tables IV and V give typical results for oxygen-15 production via the $^{15}N(p,n)^{15}O$ and $^{14}N(d,n)^{15}O$ reactions. Note that a flowing target using ^{15}N-N_2 as the target gas is not practical because of the high cost of the stable isotope (cf. Table X). Fluorine-18 is available via the $^{18}O(p,n)^{18}F$ and $^{20}Ne(d,\alpha)^{18}F$ reactions. Here it is impractical to bombard to

Table III
Carbon-11 Yields

$^{14}N_2$ Target $^{14}N(p,\alpha)^{11}C$ Threshold 2.9 MeV

$t_{1/2}$ = 20.4 Min

Energy on Target MeV	Saturation Yield mCi/μA	Yield at 20 μA mCi	Yield at 20 μA 20 Min	Practical Yield ^{11}C(75%)
17	184	3680	1840	1380
16	172	3440	1720	1290
15	154	3080	1540	1155
14	135	2700	1350	1012
13	115	2300	1150	862
12	94	1880	940	705
11	77	1540	720	540
10	62	1240	620	465
9	49	980	490	367
8	38	760	380	285
7	22	440	220	165
6	5	100	50	37

Table IV
Oxygen-15

$^{15}N_2$ Target	$^{15}N(p,n)^{15}O$	Threshold 3.5 MeV
$t_{1/2}$ = 2.1 min		
Energy on Target MeV	Saturation Yield mCi/μA	Yield at 20 μA mCi	Practical Yield 20 μA mCi
17	172	3440	1720
16	156	3120	1560
15	140	2800	1400
14	123	2460	1230
13	105	2100	1050
12	86	1720	860
11*	70	1400	700
10	60	1200	600
9	52	1040	520
8	43	860	430
7	29	580	290
6	13	260	130

* A static target with a 0.5 mil foil window will allow ~ 10.7 MeV on target. A thick target assuming no gas density reduction (i.e. 10.7 MeV to 3.5 MeV and requiring a target thickness of 133 mg/cm^3) requires about 580 cc at 20°C for a 2.54 cm internal diameter target.

Table V
Oxygen-15

$^{14}N_2$ Target	$^{14}N(d,n)^{15}O$	Threshold 0
$t_{1/2}$ = 2.1 Min		
Energy on Target MeV	Saturation Yield mCi/μA	Yield 20 μA mCi	Practical Yield 20 μA mCi	1 Min Residence Flowing Target 20 μA
10	88	1760	880	440
9	77	1540	770	385
8	65	1300	650	325
7	53	1060	530	265
6	40	800	400	200

Table VI
Fluorine-18

$^{18}O_2$ Target	$^{18}O(p,n)^{18}F$	Threshold 2.4 MeV

$t_{1/2}$ = 109.7 min

Energy on Target MeV	Saturation Yield mCi/μA	Yield at 20 μA mCi	Yield at 20 μA 2 hr	Practical Yield ^{18}F 50%
17	243	4860	2430	1215
16	236	4720	2360	1180
15	226	4520	2260	1130
14	216	4320	2160	1080
11	167	3340	1670	835
10	147	2940	1470	735
9	129	2580	1290	645
8	110	2200	1100	550
7	89	1780	890	445
6	59	1180	590	295

Table VII
Fluorine-18 Via $H_2{}^{18}O$

$H_2{}^{18}O$ Target	$^{18}O(p,n)^{18}F$	Threshold 2.4 MeV

$t_{1/2}$ = 109.7 min

Energy on Target MeV	Saturation Yield mCi/μA	Yield at 20 μA mCi	Yield at 20 μA 2 hr	Practical Yield ^{18}F 50%
16	184	3680	1840	920
15	176	3520	1760	880
14	168	3360	1680	840
13	159	3180	1090	545
11	130	2600	1300	650
10	115	2300	1150	575
9	101	2020	1010	505
8	86	1720	860	430

near saturation since it would require a beam-on time in excess of 8-10 hrs. In our experience, 1.5 to 2 hrs is optimal although for water targets 1 hr is usually sufficient. The $^{18}O(p,n)^{18}F$ reaction is particularly well suited for the preparation of ^{18}F fluoride ion and the $^{20}Ne(d,\alpha)^{18}F$, Table VIII, is useful for the preparation of ^{18}F-F_2. Both targets are simple in construction and use, delivering the needed radionuclide directly at end of bombardment. Problems involving these targets are addressed in the literature (cf. ref 1 and references therein). It should always be kept in mind when considering tables of this sort that windows are required on gas and liquid targets. Thus the maximum energy of any machine is not what is available on target. Examples of how target window thickness affects beam energy on target (energy out) is given in Table IX. Havar, a typical window material, is used as an example. For some liquid and atmospheric pressure gas targets windows as thin as 0.0006 cm can be used. However, with enriched isotopes perhaps 0.00122 cm is the best minimum thickness. When using pressurized targets, thicknesses of 0.00254 cm or greater may be required.

The art of target design and optimization of yield taking all factors into consideration, e.g. cost and complexity of target body, bombardment time necessary in light of quantity of final product required, complexity of chemistry leading to precursor, cost of target material and target material purity (cf. reference 20), and level of expertise needed to produce the product, cannot be addressed in this paper. When considering proton only reactions, target cost cannot be neglected. A list

Table VIII
Fluorine-18

^{20}Ne Target	$^{20}Ne(d,\alpha)^{18}F$	Threshold 0
	$t_{1/2}$ = 109.7 min	

Energy on Target MeV	Saturation Yield mCi/μA	Yield at 20 μA mCi	Yield at 20 μA 2 hr	Practical Yield ^{18}F 60%
10	69	1380	690	414
9	61	1220	610	366
8	51	1020	510	306
7	40	800	400	240
6	28	560	280	168

of current prices (in the U.S.A.) of enriched isotopes from commercial sources is given in Table X. Boron-11, which is useful for proton only machines, since the carbon-11 yield is higher for the $^{11}B(p,n)^{11}C$ reaction than for the $^{14}N(p,\alpha)^{11}C$ reaction at the same energy, is regrettably not readily available. The cost of a thick target for ^{13}N, ^{15}O and ^{18}F production given 10 MeV on target is given in Table XI. The cost of a water target can be cut to ~ $38.00 (0.5 g) however, even at this price recovery of target material is mandatory. This is readily appreciated given two or more production runs/day throughout the year. By way of comparison the cost of natural abundance nitrogen and neon as target gases is negligible and recovery of target is unnecessary.

One aspect of gases as targets is particularly worthy of mention here and that is the reduction of gas density as the particle beam strikes the gas. This problem, while widely addressed in the literature e.g. ref 12-19, is frequently overlooked when predictions of yield are based on what one measures in a thin target at 1 μA beam current or less. Yields cannot be estimated based on a thin or thick target yield at 1 μA by multiplying by beam current e.g. the 20 μA given in the yield table. Thus a "practical yield" is given where the reduction from theoretical is due to bombardment time, loss by density reduction and losses due to target chemistry. While thick targets can be devised, adjusting for the density reduction loss, pressure and volume are usually a limiting factor.

Table IX
Energy Loss in Havar[a] Target Windows

		Protons		Deuterons	
	Foil Thickness	Energy In	Energy Out	Energy In	Energy Out
A	0.00122 cm	17	16.8	10	9.5
	0.5 mil	16	15.8	8	7.5
		11	10.7	—	---
B	0.00254 cm	17	16.6	10	9.0
	1.0 mil	16	15.6	8	6.8
		11	10.4	—	---
C	0.0127 cm	17	15.0	10	5.4
	5.0 mil	16	13.9	8	1.3
		11	8.2	—	---

a. Havar composition Co 0.425, Cr 0.20, Fe 0.179, Ni 0.13, W 0.028, Mo 0.02, Mn 0.016

In passing from purely nuclear and physical parameters and the limitations of radionuclide production, one should then consider what is actually occurring in the target during bombardment and how the product radionuclide, whatever its form, is then converted to precursor for organic synthesis or in some cases how it is dealt with when delivered directly (e.g. as in the case of ^{15}O-O_2 gas etc.). The synthesis of precursors has been reviewed (21) and general aspects of compound synthesis have

Table X
Cost of Stable Isotopes

	Form	Enrichment	1985 Price/g of Isotope
Carbon-13	$^{13}CO_2$	90%	$ 72.40-$89.40
		99%	$ 78.90-$97.50
	$Ba^{13}CO_3$	98+%	$108.00-$133.50
Nitrogen-15	$^{15}N_2$	98+%	$135.00-$166.90
Oxygen-18	$H_2{}^{18}O$	5-10%	$ 23.80-$29.40
Oxygen-18	$H_2{}^{18}O$	95%	$ 62.10-$76.80
Oxygen-18	$^{18}O_2$	95%	$118.80-$146.90
Neon-20	Ne	99.95%	$47.30/LITER
Neon	Ne	Nat. Abund.	$ 0.09/LITER
Boron-11	H_3BO_3	98+%	NA

Table XI
Target Cost 1985 (Approximate)

10 MeV Protons on Target

Target	Material	Weight	Isotope Cost
Carbon-13 (^{13}N)	Powder	16mg	$2
Nitrogen-15 (^{15}O)	Gas	680mg	$113
Oxygen-18 (^{18}F)	Gas	821mg	$120
	Water	1g	$77

[Deuterons; Neon (^{18}F) $^{14}N(^{13}N)$: Cost, Negligible]

been addressed (22, cf. also references 1 and 2). A book discussing all aspects of compound synthesis using carbon-11, fluorine-18 and nitrogen-13 has been published (23).

Radiopharmaceutical Development and Application

Progress and some of the pitfalls in the current development and application of radiotracers for PET emphasis on quantitative methods will be described in somewhat greater detail in what follows. Examples will include oxygen-15 tracers (for blood flow, oxygen utilization, and blood volume measurements), and radiotracers for glucose metabolism, neurotransmitter studies, and protein synthesis. The section will be concluded by a short description of some of the newer, developing radiotracers, some of which may provide the basis for the PET methods of the future.

Oxygen-15 Tracers: Oxygen-15 with its 2-minute half-life is readily available on-line in the chemical forms of $[^{15}O]O_2$, $H_2[^{15}O]$, $[^{15}O]CO_2$, $C[^{15}O]$ and $N_2[^{15}O]$. A number of these radiotracers are produced by commercially available black boxes and are therefore ideally suited for clinical application at a hospital based cyclotron. Although no wet chemistry is involved in converting $[^{15}O]O_2$ produced by the target into other radiotracers, quality control of these radiopharmaceuticals is required at frequent intervals to ensure that the black boxes are functioning properly and that radiochemical purity is maintained.

Tracer kinetic models for the use of the oxygen-15 tracers for the measurement of cerebral blood flow and oxygen utilization have been well validated (24-27) and these measurements are frequently used to determine the metabolic status of diseased tissue, for example, in stroke (28) and cerebral malignancy (29). In addition, the use of oxygen-15 has certain advantages in the study of somatosensory stimulation and cognitive tasks. For example, an oxygen-15 study requires only a few minutes of cognitive performance or of stimulation thereby reducing attentional deficits which may occur during longer periods of stimulation (30).

In addition to its use in the study of stroke, cerebral malignancy, PET and oxygen-15 tracers have also recently been applied to the study of regional cerebral blood flow in severe anxiety (31) and in newborn infants at risk (32,33).

Radiotracers and Issues in the Measurement of Brain Glucose Metabolism: The ^{18}FDC method (34) which was based on the ^{14}C-2DG autoradiographic method in animals (35) is now the most frequently used PET method at cyclotron-PET centers around the world. The most widely used method of synthesis is still via electrophilic fluorination using fluorination reagents derived

from ^{18}F-labeled elemental fluorine, [^{18}F]F_2 (1, and references therein). However, the nucleophilic fluorination reactions (36) which lead to an isomerically pure product (37) in high yields and high specific activity have been described and are being used at an increasing number of institutions. In particular the increase of the reactivity of ^{18}F-fluoride using a crown ether is a noteworthy achievement which should increase the utility of fluoride in other radiotracers as well (38). This is an important development in the potential economical supply of ^{18}FDG from regional cyclotron-PET centers to user groups. ^{11}C-2DG is also being used and offers the possibility of making serial glucose metabolic measurements in a single subject at 2 hour time intervals (39). The frequently raised question of the lumped constant value in normal human brain for ^{11}C-2DG and ^{18}FDG was recently addressed by direct measurement (40). Comparative measurement of lumped constant values in diseased and normal brain tissue was made in vivo recently using sequential PET measurements of glucose transport with 3-O-[^{11}C]methyl glucose and ^{18}FDG (41). The application of the latter technique and the measurement of the LC in other disease states will be important in the widespread utility of the analog method.

A tracer kinetic model for glucose utilization using ^{11}C-labeled glucose was developed nearly a decade ago (42). ^{11}C-Glucose is now available in sufficiently high chemical and radiochemical purity for PET measurements in humans (42-44). Although its rapid metabolism in vivo requires that accurate rapid time-activity tissue and plasma measurements at early times be made, and because of this that a blood volume correction be made, ^{11}C-glucose has an advantage over the use of deoxyglucose analogs such as ^{18}FDG in that it does not require the use of a lumped constant. It is safe to say that unless a purified preparation of ^{11}C-glucose is used and time/activity data from PET is obtained at very early times after an intravenous injection of ^{11}C-glucose and unless a tracer kinetic model is correctly applied, the PET image represents uptake of carbon-11 rather than regional glucose metabolism. This point deserves emphasis in light of a number of reports of PET measurements of "brain glucose metabolism" on subjects who have injested a cocktail of irradiated spinach leaves. Again the lure of the color image, which in this case, falsely claims a relationship to glucose metabolism, seriously compromises the image of PET as a scientific tool.

Radiotracers for Neurotransmitter Studies: The study of the neurotransmitter dopamine has been approached by using labeled antagonists to the dopamine receptor or by using labeled precursors to dopamine. Dopamine itself, (45) unfortunately, does not cross the blood brain barrier. In the first approach labeled butyrophenones, antagonists to the dopamine receptor which cross

the blood brain barrier, are the most widely applied. These compounds, the most notable examples of which are spiroperidol and N-methylspiroperidol are highly selective for dopamine receptors in human and baboon (46-48, 51-56) caudate/putamen and are metabolically stable in brain tissue (56). Since the unlabeled molecules contain fluorine, labeling with ^{11}C or ^{18}F does not significantly perturb the biological properties of the labeled drug. Both ^{11}C and ^{18}F N-methylspiroperidol are currently prepared in very high specific activity, (53) an essential requirement in avoiding receptor saturation which can significantly alter time/activity curves and confuse the two different effects of receptor saturation and non-specific binding.

For the ^{11}C-labeled neuroleptics as well as for a large number of other tracers, ^{11}C-methyl iodide has emerged as an essential precursor molecule. Its synthesis has (1 and references therein) recently been streamlined (58). Another dopamine antagonist ^{11}C-raclopride (59) is also prepared via ^{11}C-methyl iodide and used to probe D_2 receptors in vivo (60). Whether in vivo N-[^{11}C]demethylation is a significant metabolic pathway depends on the structure of the molecule and the use of [^{11}C]methyl esters and N-[^{11}C]-ethyl compounds must, of course, be devoid of demethylation in the organ of interest within the time course of the study.

While ^{11}C-neuroleptics can be used to study radioligand-receptor interaction for time periods up to 90 minutes, the statistics of measurement at these later time periods rapidly degrade especially in reference areas (such as cerebellum) which are devoid of dopamine receptors. Here ^{18}F-labeled ligands (52, 56) offer a distinct advantage allowing measurements to be made with good statistics for several hours after injection providing high contrast and the measurement of important kinetic parameters. The use of the nucleophilic aromatic substitution reaction represented a breakthrough in the synthesis of ^{18}F-neuroleptics (49-51, 57). A number of models have been proposed to fit the data produced by PET measurement of radioligand-receptor interaction (55, 61,62). However, three factors, high radiotracer specific activity, high quality PET measurements, and plasma input function measurement are essential before attempting a kinetic analysis. In addition, partial volume effects especially with moderate to low resolution PET instruments may significantly change the shape of time/activity curves in small regions of interest which occur in a background of changing radioactivity.

The study of dopamine neurotransmitter systems has also been pursued using ^{18}F-labeled L-DOPA, a precursor to dopamine, which crosses the blood-brain barrier (63). Since fluorine does not

naturally occur in L-DOPA, its use as a label represents a potential perturbation in the biological behavior of the molecule. It was found that the substitution of fluorine for hydrogen on position 6 of the DOPA molecule results in the least alteration in the properties of the parent compound (64). Since the multiplicity of labeled molecules produced during normal DOPA metabolism, potentially complicates a PET image, detailed biochemical studies have been and are currently being undertaken to address the interpretation of PET studies in humans using ^{18}F-fluoro-DOPA (65,66). The distribution of ^{18}F after injection of ^{18}F-6-fluoro-DOPA (the fluorine isomer of choice) is predominantly associated with the caudate/putamen a region known to contain high concentration of dopamine and dopamine receptors (67).

The synthesis of ^{18}F-6-fluoro-DOPA has occupied the attention of a number of groups and while a number of sophisticated approaches have been explored, direct fluorination of DOPA with $[^{18}F]F_2$ is currently the method of choice even though the yield is low (68). The synthesis of carbon-11 L-DOPA labeled in the carboxyl group (69) and in the metabolically stable position 3 (70) has also been reported. Asymmetric synthesis has been explored as a route to pure L-amino acids (71). As was the case with ^{18}FDG and ^{18}F-neuroleptics, a demonstrated utility in PET studies generally initiates an increase in development work in the synthesis of a particular radiotracer.

PET Methods for Measuring Regional Brain Protein Synthesis: The measurement of regional brain protein synthesis has been approached using two different radiotracers. In one method, ^{11}C-leucine (^{11}C-carboxyl) is the radiotracer (72). The tracer kinetic model requires the label to be in the ^{11}C-carboxylic acid group of L-leucine (73). In the other method, [^{11}C-methyl]-methionine is the radiotracer and a tracer kinetic model for this tracer was validated using a triple tracer experiment (^{14}C, ^{11}C, and ^{3}H-L-methionine) in baboons (74). At fifty minutes, 50% of the ^{11}C in baboon brain was as ^{11}C-labeled protein (74). Since methionine is well known to participate in transmethylation reactions as well as protein synthesis, the possibility of complications in interpretation of PET data due to ^{11}C-labeled products other than ^{11}C-labeled protein in brain has been recently addressed in rats using tissue extraction and analysis. These studies comparing ^{11}C-leucine and ^{11}C-methionine showed that at 45 minutes after injection, 36% of the label was present as non-protein metabolites with ^{11}C-methionine whereas only 3% of the label was present as non-protein metabolites with ^{11}C-leucine (75). From this study, it was concluded that leucine provides a better measure of brain protein synthesis with PET or autoradiography.

New Radiotracers and Applications for PET: Research and development in PET continues to focus heavily on problems in the neurosciences with a special emphasis on the development of methods for probing neurotransmitter receptor:radioligand interactions. New carbon-11 labeled (76,77) and fluorine-18 (78) labeled radioligands for the opiate receptor have been reported and PET studies have begun. The benzodiazepine receptors (79) and acetylcholine muscarinic receptors (80) are also the object of a number of investigations.

The use of PET to probe in vivo pharmacokinetics has also been explored. Here transport and uptake of drugs across the blood brain barrier and kinetic profiles of uptake and egress have been measured (52, 81-84).

A new area is the development of radiotracers with an affinity for the hypoxic areas of tumors and ischemic areas of heart and brain (85).

In vivo assessment of the metabolic status of tumors continues to be an important problem. Here the tracers of glucose and oxygen metabolism play a major role. In the case of glucose metabolism, glucose metabolic rate parallels degree of malignancy (86). Considerable contrast between tumor and surrounding tissue is obtained with ^{11}C-methionine (87,88). Although the mechanism of trapping of ^{11}C-methionine has not yet been demonstrated, there does appear to be a unidirectional transport of methionine into tumor tissue (89). Another tracer, ^{11}C-putrescine, has been developed to take advantage of the increase in polyamine metabolism associated with rapidly proliferating tissue (90,91). Since uptake in normal brain tissue is very low, a high contrast between tumor and normal brain is obtained in PET studies of human cerebral malignancy with ^{11}C-putrescine.

Yet another area which has shown promise is the use of suicide enzyme inhibitors in conjunction with PET to probe the distribution of enzyme activity in vivo. Feasibility studies with the ^{11}C-labeled suicide inhibitors of monoamine oxidase type A and B (^{11}C-clorgyline and ^{11}C-deprenyl) have shown that this is a potentially fruitful new application for PET (92).

In summary, PET continues to be more critically and creatively applied not only to problems in the neurosciences (93) but to the fields of cardiology as well (94). While there are a great number of tracers being used at cyclotron-PET centers around the world, perhaps three could be categorized as standard in that not only is their use widespread and relatively routine but also they are used in conjunction with a tracer kinetic model. These are the ^{15}O-tracers (95), the deoxyglucose (^{18}FDG and ^{11}C-2DG) (10) and ^{11}C-palmitic acid (96,97). One can expect

Table XII
Requirements for Single (p) or Two Particle (p,d)
Cyclotrons with Proton Energies = 17 MeV

		Description	Cost ($)[a]	Space Requirement
1.	Cyclotron	Machine Only and RF Supply	$7x10^5$ - 1.0^6	20-60m^2
2.	Cyclotron Operating Peripherals	Control Panel Power Supplies Primary Cooling[b]	Included in (1)	20-40m^2
3.	Peripherals	Switching Magnets Auto Target Changer Beam Lines Focussing Magnets Black Boxes Gas Delivery System Rabbit System Beam Monitoring System Etc.	Variable Depends on Items $1.0x10^5$ - $6x10^5$	Included in (1)
4.	Shielding[c]	Required for all Current Machines. Local Radiation Safety Laws Apply	$2x10^5$ - $8x10^5$	1 meter to 2.5 meters of Concrete on all Sides or H_2O equivalent
5.	Laboratories	Chemistry Labs Including Shielded Space for Syntheses	---	50-300m^2

a. Costs are in U. S. Dollars, 1985.
b. Secondary cooling usually supplied by user.
c. Local architects can provide accurate estimates given local radiation safety requirements and local concrete and construction costs. In some local situations, dense concrete is more economical than normal concrete. Building underground can result in savings because wall and floor thicknesses can be reduced.

that in the very near future the neurotransmitter receptor binding radiotracers will also fall into this category since the difficult questions of biochemical validation and modeling are currently being addressed. Thus the number of compounds for which black boxes are an economical investment and can be used without a large professional staff is still limited at present. Their utility is of course the determining factor. The addition of a neuroleptic black box, be it for methylspiroperidol or some other compound, should be realized in the near future.

Economic Considerations

The cost of any installation will clearly depend on local conditions, availability of personnel, and experience in developing an infrastructure for operation of the facility including what is necessary for interpretation of data. Table XII provides some information that can be used by the reader for a crude estimate, in 1985 U.S. dollars of such costs.

There are perhaps two conditions under which cyclotron-PET centers can operate today. What is prevalent at present are centers which combine in most cases large professional staffs, biochemists, chemists, computer specialists, engineers, physicists, and physicians to serve a broadly based research function and in some cases a clinical service function. The second condition which is just now beginning to develop is the purely clinical PET center where technical personnel operate the cyclotrons, black boxes and PET machines providing the physician with a service in his dealing with the disease process in patients in much the same way that CT, NMR or the many types of radioimaging are used in hospitals today. As has already been noted, such centers will, in most cases, be dependent on the university hospitals and research centers for new radiopharmaceuticals.

A cyclotron-PET center in a university hospital or research institute has, in almost all cases, the needed technical and professional services required as backup for a broadly based research program. Included would be adequate computer facilities, machine shops, electronics shops and other mechanical and electrical services. In addition, mathematicians, chemists, biochemists, engineers, and physicians, etc., who are not part of the cyclotron-PET team but who can be consulted as required for any particular need, are convenience adjuncts to the core team. By contrast, a hospital-PET center would not have such an infrastructure and would depend primarily on the manufacturer, consultants and others for help when needed. The cyclotrons noted in Table I can all provide the needed radionuclides with the caveat that the single particle machine, regardless of energy, 11 MeV or higher, <u>requires</u> the use of enriched isotopes for three of the four accessible radionuclides.

A frequently addressed question is the number of individuals needed to support the technical aspects of a cyclotron-PET center. A survey of the cyclotron-PET centers in operation today will show a very wide range in the numbers of professionals and technical staffs involved. To consider the cyclotron as an example, staffing will depend on the factors noted above but also on local law and safety considerations. The currently available machines can be operated by one person and indeed maintained by that person given adequate professional background. However, local radiation safety law and common safety considerations have resulted in at least two individuals being needed in most installations operative today. Given the usual conditions for vacations, illness, etc., a full 8 hour day of operation requires that three individuals be experienced in the operation but not necessarily the maintenance of the machine. The majority of installations have 2 to 5 such personnel usually depending on whether in-house repair and maintenance is done or reliance for repair is placed solely on the manufacturer of the particular machine. There is little point in presenting personnel estimates for labeled tracer research and development as this will vary widely depending on the nature of the institution. Labeled tracers from a hospital clinical service machine, however, could in principal be part of the hospital radiopharmaceutical delivery service. We assume that only hospitals with well developed nuclear medicine services would consider a cyclotron-PET as part of their clinical research and clinical service function. The cyclotron-PET has not as yet developed to the point where its use is as routine as that of a CT device. However, it is our belief that given the uniqueness of the information it provides and the rapid strides being made toward simplicity of design and operation, cyclotron-PET will take its place in the armamentarium of medical practice.

CONCLUSIONS

This paper is not intended as a review of the Cyclotron-PET field. We hope that we have given the reader a conception of what some of the aspects of cyclotron-PET involve, focussing primarily on the cyclotron itself and labeled tracer preparation and application. Accelerators being developed include proton and deuteron linacs and "super conducting" (thus very small) cyclotrons. These have not yet appeared and the demands of cost, maintenance and size will determine whether they replace the conventional cyclotron.

The future looks bright and at the very least it can be stated that cyclotron-PET has given us a tool which can probe human biochemistry and its relation to the normal and pathological state in a manner not possible by any other method existing today. With the rapid advances occurring at present, its

function as a research tool will increasingly be complemented with its use in routine clinical service.

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