APPLICATIONS OF CYCLOTRONS IN MEDICAL DIAGNOSIS

D. J. Silvester

Medical Research Council Cyclotron Unit, Hammersmith Hospital, London W12 OHS, U.K.

Abstract

Some of the current medical applications of cyclotron-produced radionuclides are reviewed, and a brief comparison is made of the scope in this field of cyclotrons of different characteristics.

1. Introduction

Medical applications of cyclotrons nowadays include radiotherapy, *in vivo* activation analysis, and may, in years to come, embrace such techniques as proton beam radiography, which is the subject of other papers in this Conference. By far their widest application till now, however, has been in making a range of radionuclides, over and above those available from nuclear reactors, which are useful in a wide variety of diagnostic investigations.

The practice of medical diagnosis is the identification of disease from an examination of its symptoms. Radionuclides can help in this examination provided that they can be built into compounds ("radiopharmaceuticals") which show some degree of concentration in a specific organ or lesion, so that it may be "visualised" by detection of the γ-radiation emitted. A classic example of this is the diagnosis of bone lesions, at a much earlier stage than they could be detected by conventional X-ray techniques, through their enhanced uptake of cyclotron-produced fluorine-18 which for several years was the nuclide-of-choice for this purpose.

However, radionuclides can provide much more than just morphological data: they can tell us about the movement and metabolism of the labelled compounds themselves, and thereby about the function of the tissues through which they pass. This kind of information can be vital to the accurate diagnosis of disease, especially in situations where morphological change is minimal.

To a casual observer, the nuclear medicine scene may appear to be dominated at present by just one reactor-produced radionuclide, technetium-99m, which has physical and chemical characteristics that make it ideal for a variety of diagnostic applications, and which has the important additional features of being cheap, and obtainable virtually all around the world from commercial sources. Cyclotron products, in contrast, are seldom cheap; but where they are available they undoubtedly contribute in many ways to the solution of medical problems. As an illustration of this, Table 1 lists some 40 different medical applications of 16 radionuclides made on the M.R.C. cyclotron at Hammersmith in the past few years.

The table shows that these radionuclides range in half-life from 13 sec (^{81m}Kr) to over 4 days (^{124}I), and span the periodic table from the biologically important light elements, carbon, nitrogen and oxygen, to lead. All these products have two important features in common: the first is the emission of γ-radiation which is detectable with good spatial resolution by currently available equipment. The second is that each has some chemical characteristic which makes it suitable as a label for a particular compound, or class of compounds.

In this short paper, I naturally cannot discuss the many applications of all these radionuclides. Instead, I have selected just three topics for close attention, not only because of their medical importance, but also because they show how cyclotrons of different sizes can contribute usefully in this field.

2. Measurement of Pulmonary Oedema

Pulmonary oedema (the accumulation of extra-vascular water in the lungs) is a distressing condition which can occur frequently as a secondary effect of several disorders. Now any self-respecting doctor will tell you that he can diagnose pulmonary oedema using nothing more sophisticated than his stethoscope; but he will have difficulty in quantifying his observations, and in detecting oedema at an early stage, and therefore in assessing the response of his patients to different forms of treatment. The new method of investigation which my colleagues, Drs. Fazio, Hughes, Rhodes, Jones and Clark have developed at Hammersmith enables a quantitative assessment of oedema to be made in different regions of the lungs. The principle of the method can be seen in Fig.1.

The first step is to inject a small volume of water labelled with oxygen-15 into the patient's arm. Within a few seconds, the activity reaches the lungs, where it can be measured by scintillation counters placed over the regions of interest and curves like these represented by the solid circles can be obtained. The rising part of each curve represents the arrival of the ^{15}O-labelled water carried in the blood stream. Once in the lungs, however, the labelled water can diffuse into the extravascular water pool, and the rate at which it washes out again, represented by the falling part of the curve, will be determined by the size of that pool, relative to the size of the vascular pool.

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TABLE 1

Radionuclides in routine production at Hammersmith since 1971

Nuclide	Half-Life	Chemical Form	Application
^{15}O	2m	O_2	Regional oxygen utilisation in the brain
		CO_2	
		H_2O	Measurement of pulmonary oedema
^{13}N	10m	N_2 gas or solution	Lung ventilation and perfusion
		NH_3	Myocardial investigations
^{11}C	20m	CO	Regional and total gas exchange in the lung Spleen scanning Blood volume measurements/Pulmonary oedema
		Glucose/ fructose	Regional metabolism in diabetes
^{18}F	1.8h	Aqueous fluoride	Tracer studies Dental studies Bone scanning and bone blood flow
		Labelled amino acids	Pancreas scanning
^{43}K	22.4h	KCl	Electrolyte balance measurements Coronary blood flow measurements
^{52}Fe	8.2h	Ferric citrate	Bone marrow scanning
^{62}Zn	9.3h	$ZnCl_2$	Potential pancreas and prostate scanning agents Studies of male infertility
^{67}Ga	78h	Gallium citrate	Soft tissue tumour scanning
^{77}Br	57h	NaBr	Electrolyte balance measurements Skin and muscle blood flow studies
^{81}Rb	4.7h	RbCl	Spleen scanning and Blood flow (^{81m}Kr generators - see ^{81m}Kr)
^{81m}Kr	13s	Gas	Regional ventilation measurements
		Aqueous solution	Myocardial and cerebral blood flow studies
^{111}In	67h	Chloride	Bone marrow scanning
		DTPA	Cisternography
		Bleomycin	Soft tissue tumour scanning
^{123}I	13.3h	KI	Thyroid studies As a label for various organ specific compounds
		Hippuran	Kidney function measurements
		Rose Bengal	Liver function measurements
		Conray	Brain tumour studies
^{124}I	4.2d	KI	Detection of residual thyroid tissue during surgery
^{129}Cs	30h	CsCl	Myocardial blood flow and infarct visualisation
		Zr phosphate complex	Stomach clearance measurements
^{203}Pb	52h	$PbCl_2$	Metabolic studies

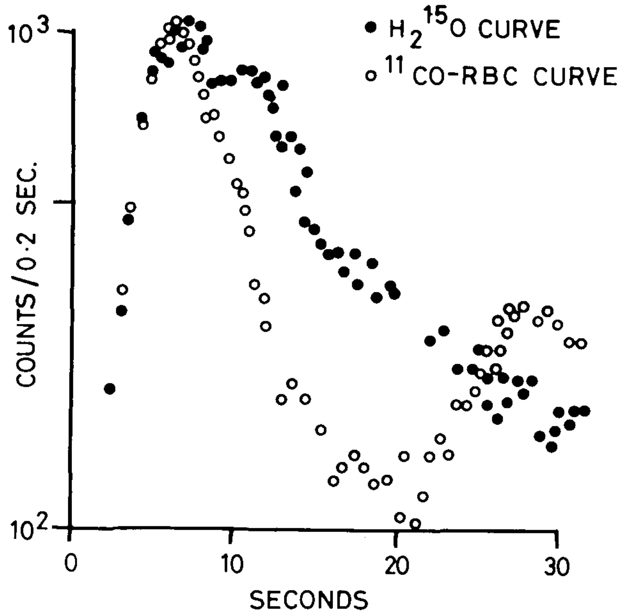

Fig.1.

The second step is to label a small volume of the patient's red blood cells with carbon-11 by exposing them to ^{11}CO. The method of doing this has been described elsewhere[1]. Upon re-injecting these labelled cells, curves like the ones shown by the open circles are obtained. This time the activity cannot diffuse into the extravascular water pool; the wash-out is more rapid, and from the difference between the two wash-out curves the size of the extravascular water pool in the region monitored can be calculated.

Fig. 2 shows the system used to make the ^{15}O-water [2]. Nitrogen gas, to which a little oxygen is added to act as a carrier, is the target material and flows from the storage cylinder shown, through the target vessel, where it is exposed to 6 MeV deuterons. ^{15}O results from the $^{14}N(d,n)$ reaction, and leaves the target vessel essentially as molecular oxygen in a stream of nitrogen. After it has passed through purification and measuring devices, a slight excess of hydrogen is added to the gas stream, which then flows through a hot palladium catalyst where all the ^{15}O is combusted to water. The water is trapped in a little saline solution whilst the nitrogen and excess hydrogen flow to waste. With deuteron beam currents of about 30 μA, up to 100 mCi of ^{15}O-H_2O can be prepared with ease in a few minutes.

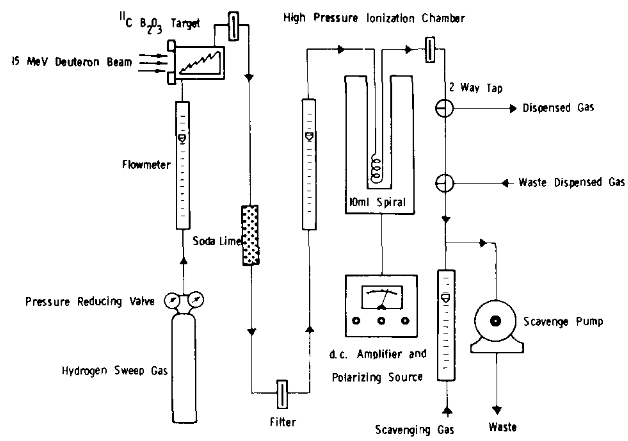

Fig.3.

Fig. 3 shows the system we use to make ^{11}CO, the red blood cell label[3]. This time the target material is Boric oxide, which, bombarded by 15 MeV deuterons, yields ^{11}C from the $^{11}B(d,2n)$ and $^{10}B(d,n)$ reactions. By passing hydrogen continuously through the target vessel during bombardment, the ^{11}C is swept out essentially in the form of ^{11}CO.

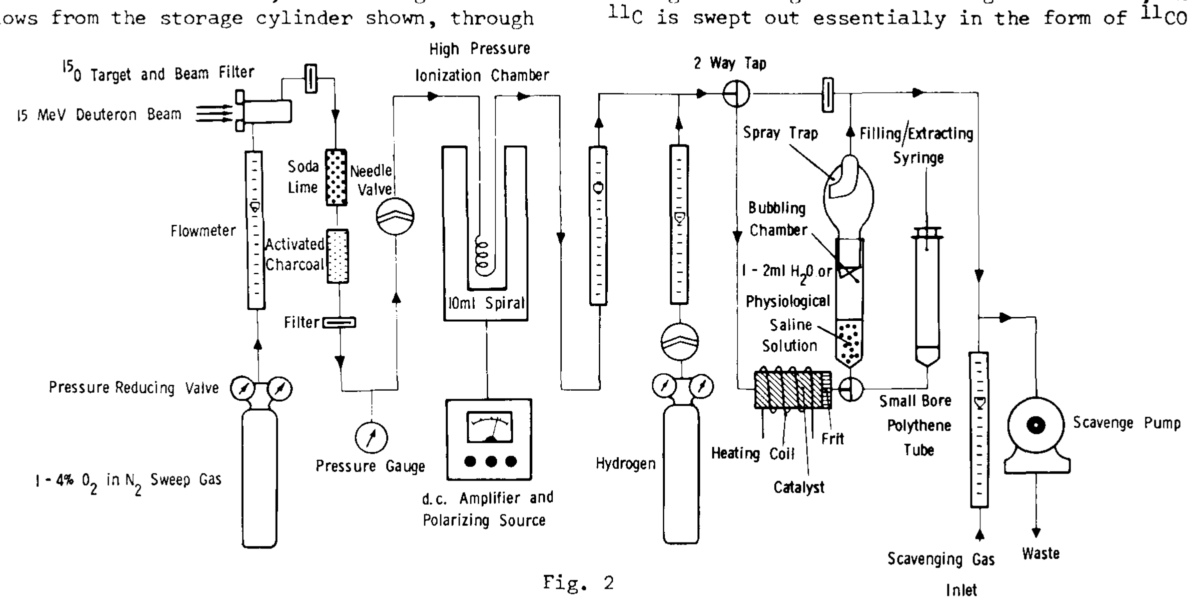

Fig. 2

(The small quantity of $^{11}CO_2$ present is removed by the soda-lime trap). Samples for labelling red blood cells are withdrawn from the gas stream as required. Again tens of milliCuries of ^{11}CO may be collected within a few minutes.

An alternative method of production uses nitrogen gas as the target material[4], carbon-11 being produced by the $^{14}N(p,\alpha)$ reaction. Although a better method in some respects, when ^{15}O and ^{11}C have to be prepared alternatively throughout a clinical session, it is obviously more convenient to use deuteron induced reactions for both.

3. Regional Ventilation Measurements

My next example is a recent diagnostic application of an ultra-short lived cyclotron product: 13 sec ^{81m}Kr. Strictly speaking, the primary cyclotron product is ^{81}Rb, the 4.5h parent of ^{81m}Kr, which is prepared by the $^{79}Br(\alpha,2n)^{81}Rb$ reaction using NaBr[5] or Cu_2Br_2[6] as the target material. The cross-section for this reaction peaks at about 30 MeV[7]. After irradiation, the ^{81}Rb is recovered in one step, using a small column of zirconium phosphate cation-exchanger. Krypton-81m can be recovered continuously from this column (on which the parent Rb-81 is retained) either in aqueous solution, or in the gas phase, as is shown in Fig.4. Which method is selected depends upon the

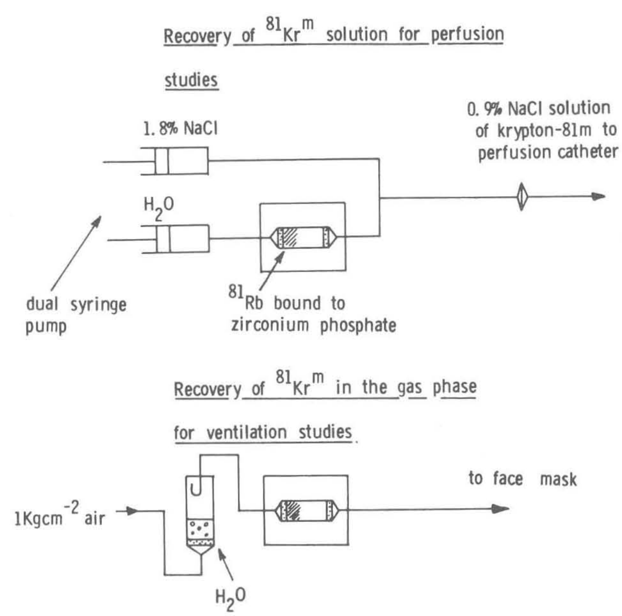

Fig.4.

nature of the clinical investigation to be undertaken. Here I shall describe only lung ventilation studies using Kr-81m in the gas phase[8]. For this purpose, the patient is positioned in front of a γ-camera and breathes air containing Kr-81m continuously through a face mask. Because its half-life is so short, an equilibrium is soon established in which the distribution of Kr-81m activity in the lungs is determined essentially only by the ventilation pattern. If a longer lived radionuclide (such as 5 day ^{133}Xe or even 10 min. ^{13}N) were used in this way, the equilibrium distribution would be influenced by gas dissolved in the blood stream, and returned by the circulatory system to regions which may be poorly ventilated, yet well perfused by blood.

Kr-81m decays be emission of 190 KeV γ-rays, and so is ideal for use in conjunction with γ-cameras. Fig.5. shows the kind of pictures

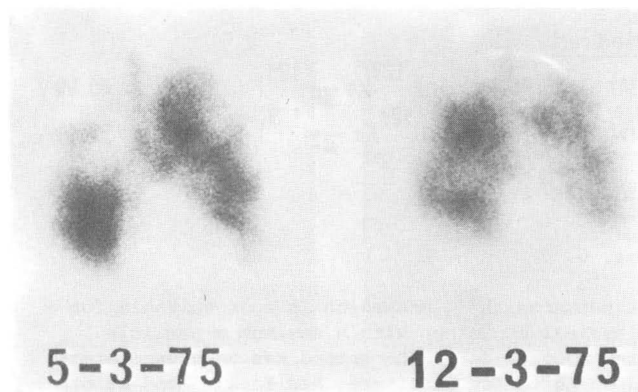

Fig. 5.

obtained from a patient with severe bronchitus. On the day of admission to hospital, the picture on the left was obtained, showing very patchy ventilation, which was especially poor in the upper right lung. After one week of treatment, the picture (on the right) is clearly improving, and three weeks later still a virtually normal ventilation pattern was seen.

4. Iodine-123

As a final example, I would draw attention to a cyclotron-product which has long been recognised as of great importance in nuclear medicine, and which features in several other papers at this Conference. I refer to Iodine-123, which decays with a half-life of 13.3h, and with the abundant emission of 159 KeV γ-rays but a negligible fraction of higher energy γ-rays. These physical characteristics make it the ideal radionuclide for *in vivo* thyroid studies, since the radiation dose it gives to patients is only about 1% of the dose given if reactor-produced I-131 is used.

The same desirable characteristics have led to several other routine diagnostic techniques being developed, using I-123 labelled compounds: notably the measurement of kidney function with labelled Hippuran, and of liver function with labelled Rose Bengal or other substances.

Iodine-123 can be made by several nuclear reactions, some of the more important being shown in Fig.6. The first reaction is the one which we use

Some reactions producing ^{123}I

Direct:

(1) $^{121}Sb\ (\alpha, 2n)\ ^{123}I$; $E_{\alpha} \simeq 25$ MeV

(2) $^{123}Sb\ (^{3}He, 3n)\ ^{123}I$; $E_{^3He} \simeq 23$ MeV

(3) $^{124}Te\ (p, 2n)\ ^{123}I$; $E_p \simeq 26$ MeV

Indirect:

(4) $^{122}Te\ (\alpha, 3n)\ ^{123}Xe \xrightarrow{\beta^+} {}^{123}I$; $E_{\alpha} \simeq 46$ MeV

(5) $^{127}I\ (p, 5n)\ ^{123}Xe \xrightarrow{\beta^+} {}^{123}I$; $E_p \simeq 58$ MeV

Fig. 6.

at Hammersmith[9], and which is most suitable for a classical cyclotron with a maximum α-particle energy of 30 MeV. The second has been used at the Sloan-Kettering Institute, New York[10] and at other laboratories where 20 - 30 MeV He-3 beams are available, and the third reaction has been used in Miami[11] and more recently at Milan[12], and Brookhaven National Laboratory[13], amongst several centres where proton beams of up to 30 MeV are available. As the figure shows, I-123 is the direct product of all these nuclear reactions, and whilst good yields may be obtained using relatively modest beam currents, they have the common disadvantage that in each case, the product is inevitably contaminated by small quantities of Iodine-124, (from $(\alpha,n)(^{3}He,2n)$ and (p,n) reactions respecitvely) no matter how highly enriched the target material may be.

Iodine-124 is a serious problem not only is it longer lived (4.2d half-life), but it emits a high proportion of high-energy positrons and γ-rays which lead to high radiation doses to patients, and to poor resolution γ-camera pictures. It can be eliminated by utilising an indirect method of production such as reactions 4 and 5 on the slide, where the primary product is Xenon-123. This can readily be isolated, and decays with a half-life of 2.1h to I-123, which can in turn be seperated and prepared for clinical use.

As the Figure indicates, however, this method of production can only be achieved by relatively big cyclotrons (the two reactions shown were first reported from Brookhaven[14] and the Crocker Nuclear[15] Laboratories respectively) so presumably pure samples of I-123 will always be relatively expensive to produce.

5. Conclusion

As Table 1 indicates, a cyclotron of quite modest energy like the one we have at Hammersmith (giving beams of only 32 MeV alphas, 16 MeV deuterons, and 8 MeV protons) is capable of serving a medical community remarkably effectively. Indeed we are able to supply several products which are not available from other sources to hospitals throughout the United Kingdom. At the same time, however, higher energy machines can undoubtedly make a much better job of producing some radionuclides (such as the example of ^{123}I which has been discussed) in good yield and in very high purity.

On the other hand, it would seem very wasteful to employ a big machine to make ^{81m}Kr-generators, and many other products of relatively low energy reactions; and of course any hospital concerned only to initiate a programme with short-lived ^{11}C, ^{13}N, ^{15}O and ^{18}F (for which there would still seem to be very great scope) would be able to do so with a machine which offered nothing more than a 6 MeV deuteron beam.

As Dr. G.O. Hendry pointed out in concluding his address on "Compact Cyclotron Engineering" at the previous meeting in this series, "if ... ^{11}C, ^{13}N and ^{15}O come into general use, there may be a demand for an ultra-compact self-shielded cyclotron for general use in hospitals". This sounds to me like a "chicken or egg" situation, but the challenge of developing such a machine[16] has been taken up by Dr. Karasawa in Tokyo and many of us are awaiting his results with great interest.

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DISCUSSION

K.V. ETTINGER: It may be worth mentioning that apart from radioisotope techniques, the activation analysis *in vivo* became applied to the medical diagnosis. It is possible to measure calcium *in vivo* in man and this technique has been used to help in diagnosis of calcium metabolism diseases in hundreds of patients. cadmium can also be determined *in vivo*, facilitating detection of chronic cadmium poisoning in industrial workers. In general, it is possible with neutron beams from cyclotrons to measure *in vivo*: H, C, N, O, P, Ca, Mn, Mg, Na, K, Fe, Cu, Cd and possibly others. The necessary fast neutron dose is within medically acceptable limits, usually between 50 mrem and 3 rem. Most of this work has been done in the Nuffield Cyclotron Laboratory in Birmingham, U.K.