# Alternative positron emission tomography with non-conventional positron emitters: effects of their physical properties on image quality and potential clinical applications

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**Abstract.** The increasing amount of clinically relevant information obtained by positron emission tomography (PET), primarily with fluorine-18 labelled 2-deoxy-2-fluoro-D-glucose, has generated a demand for new routes for the widespread and cost-efficient use of positron-emitting radiopharmaceuticals. New dual-head single-photon emission tomography (SPET) cameras are being developed which offer coincidence detection with camera heads lacking a collimator or SPET imaging with specially designed collimators and additional photon shielding. Thus, not only satellite PET imaging units but also nuclear medicine units investing in these new SPET/PET systems need to examine all available alternatives for rational radionuclide supplies from host cyclotrons. This article examines 25 "alternative" positron-emitting radionuclides, discusses the impact of their decay properties on image quality and reviews methods for their production as well as for their application in imaging techniques.

*Key words:* Positron emission tomography – Single-photon emission tomography – Positron emitters

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## Introduction

One of the most widely recognised advantages of positron emission tomography (PET) over single-photon emission tomography (SPET) is its use of the attractive positron-emitting "bio-isotopes" (carbon-11, nitrogen-13, oxygen-15) for the investigation of biological processes. Thus the difficulties of designing non-endogenous radiotracers that reliably mimic natural substrates can, in some cases, be avoided. The half-lives of these PET bio-isotopes are very short (20, 10 and 2 min, respectively), which is an advantage for imaging in humans since large amounts of radioactivity can be administered for good counting rates initially while maintaining a fairly low total absorbed radiation dose. The major disadvantage, on the other hand, is that these substances are too short-lived to be transported long distances. Thus, PET units that routinely use $^{11}C$, $^{13}N$ and $^{15}O$ must not only invest in a camera and supporting equipment, but also have access to a cyclotron and radiochemistry facilities for "on-demand" preparation of the required radiotracers. The capital investments that are needed on site are therefore heavier than for any of the other imaging techniques. This is a major reason for the technique's relative inaccessibility. If the sensitive biochemical assays that are possible with PET [1] are to become more feasible for routine imaging units, more cost-effective constellations must be found.

The $\beta^+$-emitting radionuclide fluorine-18 ($t_{1/2}$=1.8 h) can be produced in good yields even with low-energy cyclotrons. It is often used in labelling reactions to generate analogues of compounds in which a C–H or C–OH bond has been replaced with a C–$^{18}F$ bond. These tracers are, of course, somewhat more transportable than those labelled with the shorter-lived bio-isotopes. 2-Deoxy-2-fluoro-D-glucose labelled with $^{18}F$ ([$^{18}F$]FDG) is by far the most widely used of the $^{18}F$-labelled tracers. Methods for its synthesis are well validated [2] and they have also been automated for production of larger amounts to supply imaging units without their own tracer production units. With optimised scheduling, it is possible to deliver useful amounts of [$^{18}F$]FDG even after several hours of transportation by air. [$^{18}F$]FDG has become more and more important, particularly in imaging various cancer diseases, since its uptake reflects functional behaviour rather than morphological structures. Thus PET/[$^{18}F$]FDG studies may well add important information and, in some cases, even replace alternative morphological modalities such as computed tomography

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(CT), magnetic resonance imaging (MRI) and ultrasound. An extensive review on oncological applications of [$^{18}$F]FDG (≈75% of all clinical applications) has recently been presented in this journal [3], and its diagnostic value in other clinical studies, especially in the heart, is well documented [4–12].

The advantages of [$^{18}$F]FDG have generated a considerable demand for equipment that will allow its use outside large, established PET centres. Manufacturers of not only PET but also SPET cameras have recognised the need to adapt detector systems to meet the demands of this market. Most SPET camera manufacturers now offer specially designed collimators and additional camera shieldings for the performance of non-coincidence SPET with 511 keV photons from [$^{18}$F]FDG. During the last 2–3 years, coincidence systems based on conventional dual-head SPET cameras have also been designed and manufactured. However, most of the prototype cameras were based on thin, 9.3 mm (3/8″), NaI(Tl) scintillators, optimally designed for SPET and 140 keV-photons, and, therefore, had a very low photo-peak detection efficiency (around 12%) for 511 keV photons. Since the detection efficiency at coincidence imaging is the square of the detection efficiency for each camera head, a maximum "true" coincidence rate of only about 1% of the incident annihilation photons (in addition to disturbing contributions from scattered and random coincidences) could be achieved with these cameras. In order to achieve a "true" coincidence count rate of some thousands/s at such a low detection efficiency, each camera head must be able to handle several hundred thousands of single photo-peak events and a million or more total events. This required a basic redesign of the old camera electronics. A review on the properties of and problems encountered when using conventional dual-head cameras for single and coincidence detection of PET radionuclides has recently been presented [13]. Even though data on the imaging properties of newly designed dual-head coincidence systems are rarely published, their spatial resolution may be as good as 4–6 mm (FWHM) [13, 14] and clinical "coincidence" [$^{18}$F]FDG images with acceptable PET quality are regularly presented.

Most of the recently developed dual-head coincidence cameras are constructed with thicker scintillators [16 mm (5/8″) or 19 mm (3/4″)], giving a photo-peak coincidence counting efficiency that is of the order of 4 times higher. The new electronics of these cameras permit single-head count rates of the order of 1–2 million counts/s even though dead-time distortion may occur at these high rates. Using [$^{18}$F]FDG, for instance, which has no additional γ's, the total coincidence rate may be of the order of 70 000 at a single count rate of around 1.5 $10^6$/s per head. After removal of "out-of-window", scattered and random coincidences, a "true" coincidence rate of around 12 000–15 000/s remains. Although this is a useful count rate for many clinical applications using [$^{18}$F]FDG, difficulties may occur when these systems also have to handle additional γ's emitted when other positron-emitting radionuclides are used for combined PET/SPET applications. Another drawback of the larger scintillator thickness is that the intrinsic spatial resolution in SPET is impaired by some 1–1.5 mm.

Various manufacturers and research groups are presently working on alternative scintillators, such as YSO (yttrium oxyorthosilicate) and LSO (lutetium oxyorthosilicate), (Siemens/CTI) with much higher photon attenuation properties, a light yield that approaches that of NaI(Tl) and a light decay time of 70 and 40 ns, respectively. If these new scintillators are successfully employed, cameras with much higher detection efficiency and less contribution from disturbing scattering and random events may be a welcome present to the nuclear medicine community in time for the year 2000.

However, considering the use of these new camera systems, access to [$^{18}$F]FDG may not always be sufficient to meet the requirements of nuclear medicine departments stemming from clinical pressure. Constellations must be found that avoid the costs of buying and installing a dedicated cyclotron for radionuclide deliveries ($1.5–2 million with additional supplies and service contracts costing as much as $0.25–0.5 million annually) [15]. By using other, more long-lived radionuclides that can be transported greater distances from a "host" accelerator facility or by using exclusively generator-produced isotopes [16–20], the complexities associated with routine in-house radionuclide productions might be avoided, capital expenses reduced, and the number as well as cost of trained personnel and expert scientists minimised [15, 21, 22]. Although such organisations have traditionally been considered to be less flexible than those with a dedicated cyclotron, use of "alternative" radionuclides presents a number of interesting possibilities not currently routinely pursued by more conventional PET units. Such possibilities might be considered for covering the cost of acquiring new camera technologies and might be used to extend the applications of currently functioning PET satellite units.

The spectrum of physiological processes that might be studied expands as the types of radioactive element available increase. For example, the in vivo investigation of cation fluxes requires a cationic tracer (as $^{82}Rb^+$ for $K^+$). A number of cationic radionuclides can be produced by generators (rubidium-82, copper-62, gallium-68, manganese-52m and indium-110) which can be supplied by more or less remote host facilities [16, 17, 20]. Formulation or kit-type complexation to synthesise a variety of radiotracers is subsequently performed on site. The half-lives of these radionuclides span a similar range to those of the bio-isotopes. Thus, it is interesting to consider whether they, as properly designed tracer molecules, might be used to meet some of the requirements of lower cost satellite imaging centres.

Studies of slow biochemical processes may require access to radionuclides that are more long-lived than the PET bio-isotopes. For example, recent advances in the use of monoclonal antibodies and related radioimmuno-

**Table 1.** Radionuclide generators and the half-lives of their parent and positron-emitting daughters considered for clinical use by satellite imaging units

| Radionuclide | Generator | | Parent half-life, $t_{1/2}$ | Daughter half-life, $t_{1/2}$ |
|---|---|---|---|---|
| | Parent | Daughter | | |
| $^{52m}$Mn | $^{52}$Fe | $^{52m}$Mn | 8.28 h | 21.1 min |
| $^{62}$Cu | $^{62}$Zn | $^{62}$Cu | 9.26 h | 9.74 min |
| $^{68}$Ga | $^{68}$Ge | $^{68}$Ga | 271 days | 1.14 h |
| $^{82}$Rb | $^{82}$Sr | $^{82}$Rb | 25.6 days | 1.27 min |
| $^{110}$In | $^{110}$Sn | $^{110}$In | 4.11 h | 1.15 h |
| $^{118}$Sb | $^{118}$Te | $^{118}$Sb | 6.00 days | 3.6 min |
| $^{122}$I | $^{122}$Xe | $^{122}$I | 20.1 h | 3.62 min |

**Table 2.** Decay modes and the positron yields (%) for the selected PET radionuclides considered in the review

| Radionuclide | Half-life ($t_{1/2}$) | $\beta^+$-yield | Daughter product | $t_{1/2}$ daughter | Comments |
|---|---|---|---|---|---|
| *Generator-produced radionuclides* | | | | | |
| $^{52m}$Mn | 21.1 min | 97 | $^{52}$Cr | Stable | One branch (1.81%) decays to $^{52}$Mn via IT |
| $^{62}$Cu | 9.74 min | 97 | $^{62}$Ni | Stable | |
| $^{68}$Ga | 68.1 min | 89 | $^{68}$Zn | Stable | |
| $^{82}$Rb | 1.27 min | 95 | $^{82}$Kr | Stable | |
| $^{110}$In | 1.15 h | 62 | $^{110}$Cd | Stable | |
| $^{118}$Sb | 3.5 min | 74 | $^{118}$Sn | Stable | |
| $^{122}$I | 3.63 min | 77 | $^{122}$Te | Stable | |
| *Cyclotron-produced radionuclides* | | | | | |
| $^{18}$F | 1.83 h | 97 | $^{18}$O | Stable | |
| $^{34m}$Cl | 32.2 min | 54 | $^{34}$S (55%) | Stable | |
| | | | $^{34}$Cl (45%) | 1.53 s | $^{34}$Cl-branch decays by $\beta^+$ (100%) to $^{34}$S |
| $^{38}$K | 7.64 min | 100 | $^{38}$Ar | Stable | |
| $^{51}$Mn | 46.2 min | 97 | $^{51}$Cr | 27.7 days | $^{51}$Cr decays to $^{51}$V (stable) |
| $^{52}$Mn | 5.59 days | 29 | $^{52}$Cr | Stable | |
| $^{52}$Fe | 8.28 h | 56 | $^{52m}$Mn | 21.1 min | Daughter of $^{52m}$Mn is $\beta^+$-emitting |
| $^{55}$Co | 17.5 h | 76 | $^{55}$Fe | 2.6 years | Long $t_{1/2}$ of daughter |
| $^{61}$Cu | 3.41 h | 61 | $^{61}$Ni | Stable | |
| $^{64}$Cu | 12.7 h | 18 | $^{64}$Ni, $^{64}$Zn | Stable | |
| $^{72}$As | 1.08 days | 88 | $^{72}$Ge | Stable | |
| $^{75}$Br | 1.62 h | 71 | $^{75}$Se | 120 days | Long $t_{1/2}$ of daughter |
| $^{76}$Br | 16.2 h | 54 | $^{76}$Se | Stable | |
| $^{82m}$Rb | 6.47 h | 23 | $^{82}$Kr | Stable | |
| $^{83}$Sr | 1.35 days | 24 | $^{83}$Rb | 83 days | $^{83}$Rb decays to $^{83}$Kr (stable) via $^{83m}$Kr (1.86 h) |
| $^{86}$Y | 14.7 h | 33 | $^{86}$Sr | Stable | |
| $^{89}$Zr | 3.27 days | 23 | $^{89m}$Y | 16 s | $^{81m}$Y decays to $^{89}$Y (stable) |
| $^{94m}$Tc | 52.0 min | 70 | $^{94}$Mo | Stable | |
| $^{120}$I | 1.35 h | 46 | $^{120}$Te | Stable | |
| $^{124}$I | 4.18 days | 23 | $^{124}$Te | Stable | |

therapy favour the use of long-lived radioisotopes in tumour diagnosis and therapy. It has also been argued [23] that the only feasible means of accurately studying receptor sites present in low concentrations is by using very high affinity ligands labelled with long-lived isotopes that permit the "wash-out" phase to be analysed. In late images of long-lived radiotracers the receptor-bound tracer should dominate the images, while with shorter-lived isotopes the non-specific binding may be considerable and must be accounted for. The newest generation of high-resolution PET scanners with 3-D data collection and image reconstruction capabilities makes increased use of long-lived radionuclides more acceptable, since much lower amounts of injected radioactivity are required for comparable images. It is worthwhile to examine the imaging properties of such long-lived alternative radionuclides for possible use in PET as well as dual-head SPET "coincidence" cameras.

The present constellations of a host accelerator facility with satellite PET imaging units might conceivably come to encompass SPET/PET facilities. However, if this development is to improve the nuclear medicine

techniques currently in practice, tough requirements must be made on the imaging properties of the cameras as well as their accessibility. Descriptions of their accuracy and sensitivity must also take into consideration the properties of the radionuclides used. Very few PET radionuclides have imaging characteristics as attractive as those of $^{18}$F.

Radiotracers labelled with the radionuclides discussed in this review complement the arsenal of tracers labelled with the more conventional "bio-isotopes". For clinical imaging units, two routes for obtaining $\beta^+$-emitting radionuclides should be considered: radionuclide generators and direct access to a cyclotron. Some generators for "alternative" $\beta^+$-emitting radionuclides considered for clinical use are presented in Table 1. The decay schemes for their daughter nuclides as well as for the other cyclotron-produced radionuclides discussed in this paper are listed in Table 2, with data from *Table of isotopes* [24, 25].

The "alternative" $\beta^+$-emitting radionuclides have often been developed with the idea of opening new avenues for centres with or without a cyclotron to perform new basic research and clinical evaluations as well as to better exploit the unique characteristics of the PET technique. The production of most of these alternative nuclides requires medium→high energy (>20 MeV) beam lines although a few can be performed with low-energy (<20 MeV) cyclotrons. For PET centres which already have access to a dedicated accelerator, we hope this review will provide an insight into the potential of these radionuclides for new implementations of PET. We also hope that this review will serve as a basis for discussions on the operative design of satellite imaging units in the vicinity of potential host accelerators. Below we briefly describe these "non-conventional" $\beta^+$-emitting radionuclides along with their main physical and chemical characteristics, and, by no means exhaustively but hopefully representatively, review their applications in imaging techniques to date.

## Physical properties of the radionuclides

Apart from their bio-compatibility, the PET bio-isotopes have a number of other qualities that make them attractive for imaging applications. They are all short-lived and decay to non-radioactive daughters. Therefore, they can be administered in relatively large amounts without exposing patients or volunteers to high radiation doses. Secondly, their positron energies are less than 2 MeV, resulting in an intrinsic loss of spatial resolution of less than 2 mm due to the positron range. Finally, they do not emit additional $\gamma$'s which may contribute to additional random coincidences or pile-up problems in the electronics. An examination of potential utility of other radionuclides for low-cost units should consider these basic physical properties as well as the biodistribution of the labelled tracer molecules.

The intrinsic loss of spatial resolution due to the uncertainty in distance between the origins of positron emission and of positron-electron annihilation may be a disturbing factor in applications requiring high resolution (i.e. relatively small regions of interest). Annihilation occurs when the positron has sufficiently slowed down from its high initial speed in order to interact with its anti-particle, the electron. The larger the positron energy, the larger will be the average distance that it travels before annihilating and consequently, the larger the impairment of the spatial resolution. This intrinsic effect is characteristic for the radionuclide and is independent of the design and imaging properties of the PET cameras.

For assessment of the loss of spatial resolution for the radionuclides listed in Table 2, the positron transmission in tissue was assumed to obey a monoexponential expression, $N=N_0 \exp(-\mu x)$ where $\mu=1.7E_{\beta max}^{-1.14}$ is the mass absorption coefficient and $x$ is the distance in matter [26]. An average positron range $R$ in soft tissue may be assessed by $1/\mu$ and the associated estimated intrinsic loss of spatial resolution, $2R$, is listed for each radionuclide in Table 3, as well as its maximum $\beta^+$ energy and its relative yield of positron emission. Data for maximum energy were obtained from the *Table of isotopes* [24]. When positrons of different energy are emitted, their ranges were weighted with their relative yield in order to estimate some average intrinsic loss of resolution.

Another factor which must be considered is whether additional $\gamma$-rays are emitted along with the positrons at the decay. Even though PET cameras have some energy discrimination that rejects photons with energies outside a selected energy window, interference between 511 keV annihilation photons and other photons may still occur. PET cameras based on NaI(Tl) have an advantage over BGO cameras due to their better energy resolution and are thus capable of operating with a narrow discrimination window (450–550 keV). On the other hand, the slow light decay of NaI(Tl) ($\tau$=230 ns) demands a large pulse integration time during which disturbing photon interference may occur. Since the single count rate capability of NaI(Tl) is limited to somewhere in the range of 1.5–2.5 million/s, the emission of additional $\gamma$'s along with annihilation photons may limit the activity that can be administered, resulting in more randoms at the expense of a reduced "true" coincidence rate.

Values for the total $\gamma$-ray energy as well as for some principal photon lines and their yields are presented for each radionuclide in Table 3 with data from the *Table of isotopes* [25]. As compared to $^{18}$F and the bio-isotopes, some radionuclides (and daughter products) emit a large fraction of additional photons which, as mentioned above, may cause severe complications due to pile-up or random events in coincidence detection. The use of such nuclides will also introduce problems for SPET imaging due to septa penetration by the high-energy photons emitted.

The applicability of PET has been been dependent on the facts that sufficiently large amounts of the very

**Table 3.** Intrinsic physical properties of alternative PET radionuclides with impact on image quality in PET and SPET

| Radionuclide | $E_{\beta^+ max}$ (MeV) | Intrinsic spatial resolution loss (mm) | γ-energy released/ decay (keV) | Principal γ-energies (MeV) and yield [%] | Comments |
|---|---|---|---|---|---|
| *Generator-produced radionuclides* | | | | | |
| $^{52m}$Mn | 2.63 | 3.5 | 1422 | 1.43 (98%) | |
| $^{62}$Cu | 2.93 | 4.0 | 7 | – | |
| $^{68}$Ga | 1.90 | 2.4 | 38 | 1.08 (3%) | |
| $^{82}$Rb | 3.35 | 4.7 | 118 | 0.777 (13%) | |
| $^{110}$In | 2.25 | 3.0 | 929 | Complex 0.60–3.8<br>0.658 (98%) | |
| $^{118}$Sb | 2.70 | 3.6 | 51 | – | |
| $^{122}$I | 3.12 | 4.3 | 160 | 0.564 (18%) | |
| *Cyclotron-produced radionuclides* | | | | | |
| $^{18}$F | 0.635 | 0.7 | – | – | |
| $^{34m}$Cl | 2.47 (0.57)<br>1.35 (0.43) | 2.6 | 1561 | 0.146 (41%)<br>2.12 (42%)<br>and more | Additional contribution from $^{34}$Cl-positrons ($E_{\beta^+}$=4.5 MeV). No γ-rays |
| $^{38}$K | 2.60 | 3.5 | | 2.17 (100%) | |
| $^{51}$Mn | 2.21 | 2.9 | – | – | |
| $^{52}$Mn | 0.575 | 0.63 | 3156 | 0.744 (90%)<br>0.935 (95%)<br>1.43 (100%) | >1000% γ-rays per $\beta^+$ decay |
| $^{52}$Fe | 0.804 | 0.92 | 174 | 0.169 (98%) | Additional contribution from $^{52m}$Mn |
| $^{55}$Co | 1.50 (0.58)<br>1.04 (0.42) | 1.6 | 1221 | 0.48 (20%)<br>0.93 (75%)<br>1.41 (17%) | |
| $^{61}$Cu | 1.22 | 1.5 | 199 | 0.283 (13%)<br>0.656 (11%) | |
| $^{64}$Cu | 0.657 | 0.73 | – | – | |
| $^{72}$As | 3.32 (0.20)<br>2.49 (0.80) | 3.6 | 881 | Complex 0.05–3.99<br>0.834 (80%) | |
| $^{75}$Br | 1.74 | 2.2 | 473 | Complex 0.11–0.89<br>0.286 (92%) | |
| $^{76}$Br | 3.98 (0.18)<br>3.44 (0.88) | 5.3 | 2226 | Complex 0.21–4.6<br>0.559 (74%) | |
| $^{82m}$Rb | 0.800 | 0.91 | 2530 | 0.554 (63%)<br>0.776 (85%)<br>and more | >300% γ-rays per $\beta^+$ decay |
| $^{83}$Sr | 1.23 (0.90)<br>0.803 (0.10) | 1.4 | 540 | Complex 0.04–2.1<br>0.762 (30%) | |
| $^{86}$Y | 2.34 (0.04)<br>2.02 (0.15)<br>1.60 (0.21)<br>1.25 (0.45)<br>1.04 (0.15) | 1.8 | 3252 | Complex 0.132–3.9<br>1.08 (83%)<br>1.15 (31%)<br>and more | >600% γ-rays per $\beta^+$ decay |
| $^{89}$Zr | 0.897 | 1.0 | <25 | – | Additional contribution from $^{89m}$Y |
| $^{94m}$Tc | 2.47 | 3.3 | 1226 | Complex 0.87–3.9<br>0.871 (94%) | |
| $^{120}$I | 4.60 (0.42)<br>4.03 (0.30)<br>2.49 (0.15)<br>1.54 (0.05) | 5.4 | 4471 | Complex 0.42–3.1<br>0.56 (99%)<br>0.60 (87%) | >600% γ-rays per $\beta^+$ decay |
| $^{124}$I | 2.13 (0.49)<br>1.53 (0.46)<br>0.808 (0.05) | 2.3 | 852 | Complex 0.19–3.0<br>0.602 (61%) | |

**Table 4.** The effective dose per MBq for some alternative PET radionuclides and some selected SPET radionuclides at biological half-lives of 1 h, 10 h and 100 h. The values must be used with caution since they are calculated assuming complete uniform distribution of the radionuclides in man. Doses from daughter products are not included in the values

| Radionuclide | Effective dose constant mSv/MBq-h $\times10^{-3}$ | Effective dose (mSv/MBq) $T_b$=1 h $\times10^{-3}$ | Effective dose (mSv/MBq) $T_b$=10 h $\times10^{-3}$ | Effective dose (mSv/MBq) $T_b$=100 h $\times10^{-3}$ | Comments |
|---|---|---|---|---|---|
| *Generator-produced PET radionuclides* | | | | | |
| $^{52m}$Mn | 16.3 | 6.11 | 7.98 | 8.23 | |
| $^{62}$Cu | 13.4 | 2.69 | 3.08 | 3.12 | |
| $^{68}$Ga | 8.93 | 6.85 | 13.2 | 14.5 | |
| $^{82}$Rb | 14.6 | 0.428 | 0.436 | 0.437 | |
| $^{110}$In | n.a. | – | – | – | |
| $^{118}$Sb | 9.7 | 0.766 | 0.805 | 0.81 | |
| $^{122}$I | 13.0 | 1.08 | 1.13 | 1.14 | |
| *Cyclotron-produced PET radionuclides* | | | | | |
| $^{18}$F | 5.37 | 5.00 | 12 | 13.9 | [$^{18}$F] FDG EDEq=27×10$^{-3}$ mSv/MBq |
| $^{34m}$Cl | n.a. | – | – | – | |
| $^{38}$K | 18.7 | 3.03 | 3.38 | 3.42 | |
| $^{51}$Mn | 10.6 | 6.64 | 10.9 | 11.7 | +$^{51}$Cr (EDEq=260×10$^{-3}$ mSv/MBq) |
| $^{52}$Mn | 11.2 | 16.0 | 150 | 924 | High doses at long biological half-life |
| $^{52}$Fe | 4.00 | 5.14 | 26.1 | 44 | +$^{52m}$Mn. Large discrepancy with ICRP 53 (1000×10$^{-3}$ mSv/MBq) |
| $^{55}$Co | 9.72 | 13.2 | 89.1 | 208 | +$^{55}$Fe (2.7 years) EDEq=5900×10$^{-3}$mSv/MBq |
| $^{61}$Cu | n.a. | – | – | | |
| $^{64}$Cu | 1.59 | 2.12 | 12.8 | 25.8 | |
| $^{72}$As | 13.7 | 19.0 | 142 | 407 | High doses at long biological half-lives |
| $^{75}$Br | 7.85 | 7.01 | 15.8 | 18.1 | +$^{75}$Se (120 d). EDEq=3500×10$^{-3}$mSv/MBq |
| $^{76}$Br | 12.5 | 16.9 | 111 | 250 | |
| $^{82m}$Rb | 9.94 | 12.3 | 54.8 | 83.6 | |
| $^{83}$Sr | 3.61 | 5.04 | 39.7 | 127 | +$^{83}$Rb (83 days) and $^{83m}$Kr doses |
| $^{86}$Y | n.a. | – | – | – | |
| $^{89}$Zr | n.a. | – | – | – | |
| $^{94m}$Tc | 12.0 | 8.06 | 13.9 | 15 | |
| $^{120}$I | n.a. | – | – | – | |
| $^{124}$I | 4.91 | 7.00 | 64.3 | 354 | High doses at long biological half-lives |
| *SPET radionuclides* | | | | | |
| $^{99m}$Tc | 0.575 | 0.710 | 3.11 | 4.69 | |
| $^{131}$I | 2.77 | 3.97 | 37.9 | 263 | High doses at long biological half-lives |
| $^{111}$In | 1.73 | 2.46 | 21.7 | 101 | |

n.a., *Not available;* EDEq, *effective dose equivalent from ICRP 53*

short-lived bio-isotopes can be administered to maintain low noise and that repeated studies can be performed without unacceptably high radiation doses. When utilising more long-lived positron-emitting radionuclides for clinical applications, dosimetry considerations may become a limiting factor. First, it should be remembered that the doses delivered by positrons (apart from the annihilation radiation) are as large as those delivered by negatrons (beta particles) of the same energy and that $\beta^-$ emitting radionuclides are only rarely used in routine nuclear medicine imaging because of the high radiation doses. Secondly, in most clinical applications, the doses increase with increasing physical half-life and with the emission of additional $\gamma$-rays.

The estimated radiation doses per administered activity, mSv/MBq, are presented in Table 4 for most of the radionuclides considered for clinical use in this paper. Values are calculated for three alternative biological half-lives: 1 h, 10 h and 100 h. All calculations were based on a uniform distribution of the radionuclide in the whole body of an adult standard man and the values represent the effective dose (ED). These values were calculated by using the effective dose constants (mSv/MBq-h) obtained from the MIRDOSE 3 software package [27].

The values presented in Table 4 may differ considerably from those obtained in practice due to a different biological behaviour and alternative tissue concentra-

tions of the actual radiopharmaceutical. However, they may still be used to indicate when caution is recommended due to potentially high doses. The doses from the daughter radiation are not included in the tabulated values. Values for the dose/unit of activity of daughter products are indicated by values for the effective dose equivalent (EDEq) obtained from ICRP 53. Even though the build-up of daughter activity may be only a small fraction of that of the parent for long-lived daughter nuclides, it may still have to be considered in the dose estimates performed prior to clinical trials, especially when the biological half-life of both the parent and the daughter are long.

## Properties of the non-conventional positron emitters and their applications as imaging agents

*Rubidium-82*

$^{82}$Rb is a short-lived (1.27 min) $\beta^+$-emitter (95%) produced by the electron capture decay of $^{82}$Sr ($t_{1/2}$=25.6 days). The availability of this generator system, the most widely used in PET, has been an important factor in the establishment and operation of facilities which, for economic or space reasons, cannot support an in-house cyclotron. The short half-life of $^{82}$Rb has made the performance of multiple study protocols feasible even at such imaging units. Test-retests improve the reliability of the results obtained and sequential studies increase the probability that dynamic changes in ongoing pathological processes will be detected and that effects of therapeutic measures can be directly observed. However, the $\beta^+$ energy of $^{82}$Rb is high (3.35 MeV), giving an intrinsic loss of spatial resolution of almost 5 mm (FWHM), which can be a disadvantage in imaging small areas of altered uptake. On the other hand, the number of additional $\gamma$'s introducing undesired random events is quite low (13%).

In vivo applications of $^{82}Rb^+$ are based on its ability to mimic the behaviour of the potassium cation [28]. Like $^{201}Tl^+$, it is extracted by the myocytes by the $Na^+$-$K^+$-ATPase pump, enters the potassium pool and is actively retained in intact cells. The first-pass extraction is high (70%–80%) for most tissues and the rate of clearance is slow compared with that of its physical decay. The $^{82}Rb^+$ uptake is therefore related to blood flow, the $Na^+/K^+$-ATPase pump and the cell membrane integrity.

$^{82}Rb^+$, proposed as an alternative to $[^{13}N]NH_3$ for measurement of myocardial blood flow [29–32], has primarily been used for imaging functional changes related to myocardial infarction. High accuracy in detecting and assessing the function of areas with perfusion abnormalities, with or without vasoactive stress, has been reported [33–44]. Myocardial cell membrane integrity and viability have also been evaluated since $^{82}Rb^+$ is rapidly cleared from irreversibly damaged tissue, but is retained in reversibly damaged and viable tissue [35, 42, 45–47]. In several studies using $^{82}Rb^+$ and PET, patients predicted to benefit from coronary revascularisation could be identified, cardiac risks were stratified and restenoses were diagnosed [48–51]. $^{82}Rb^+$ has been used to detect coronary collaterals [52, 53], in discriminating between hibernating but viable myocardium and scar [54] and in studies of angina pectoris [55–57]. Absolute regional myocardial blood flow has been assessed using $^{82}Rb^+$ and Saperstein's method [58]. $^{82}Rb^+$ perfusion studies and metabolic studies using [$^{18}$F]FDG (available from in-house or external facilities) were found to be comparable in the assessment of myocardial necrosis/viability. Decreases in glucose metabolism paralleled losses in membrane integrity for trapping $^{82}Rb^+$ [42]. Rationales for and implications of bolus versus infusion administration of $^{82}Rb^+$ have been reviewed by Jones [59]. The spatial and temporal reproducibility of $^{82}Rb^+$ myocardial studies has been evaluated [60]. Myocardial blood flows using $^{82}Rb^+$ have also been absolutely quantified, which might be important for those cases in which the abnormal flows are homogeneous [61, 62].

Although $^{82}Rb^+$ has been primarily used in studies of myocardial perfusion, other organs have also been examined. Tamaki and collaborators reported [63, 64] that repetitive imaging with $^{82}Rb^+$ could be used to detect acute changes in renal perfusion and the flows measured with $^{82}Rb^+$ correlated well with those determined using microspheres [65]. First-pass $^{82}Rb^+$ extraction has also been used to estimate skeletal muscle perfusion [66] and to detect plasma cell granuloma in the lung [67].

The intact blood-brain barrier (BBB) is highly impermeable to $K^+$. In normal cerebral tissue the $^{82}Rb^+$ extraction fraction can only be quantitated for regions as large as a cerebral hemisphere [68]. However, when the BBB is disrupted, its permeability for cations increases. $^{82}Rb^+$ has therefore been used to investigate qualitatively and quantitatively the integrity of the BBB, particularly in the delineation of brain tumours, and, after radiation therapy, to discriminate radiation necrosis from tumour recurrence [68–76].

The use of $^{82}Rb^+$ has been more extensively discussed in [77–79]. A cost-benefit analysis for the clinical implementation of $^{82}Rb^+$ has been presented [80, 81]. $^{82}Rb^+$ was reported to be clearly superior to $^{201}Tl^+$ with regard to diagnostic potential as well as patient management. It was proposed that implementation of a rational $^{82}Rb^+$ program would lower medical expenses and social costs and increase the quality of medical care. The clinical impact of $^{82}Rb^+$/PET has been illustrated in a number of large patient studies that have demonstrated its high diagnostic accuracy in detecting coronary artery disease [43, 48, 49, 82–85].

Strontium-82 has been produced for $^{82}Rb^+$ generator production by the high-energy (800 MeV protons) spallation of a molybdenum target [86] or by the irradiation (p,xn) of RbCl with 85–51 MeV protons [87] or Rb metal with 60 MeV protons [88]. $^{82}$Rb is obtained for bolus administration and for continuous elution from a porta-

ble generator [89–100]. Due to the 25-day half-life of the parent nuclide, this generator needs to be replaced every 1–2 months, depending on the calibration activity in relation to the utility. Radiation doses for PET studies with $^{82}Rb^{+}$ have been estimated previously [101].

*Gallium-68*

$^{68}Ga^{3+}$ ($\beta^{+}$=89%, $t_{1/2}$=68.1 min, $E_{\beta+max}$=1.90 MeV) is usually obtained through the electron capture decay of germanium-68 ($t_{1/2}$=271 days), absorbed on an appropriate solid phase (i.e. generator produced). The half-lives of both the mother and daughter nuclides, as well as the other physical properties, are favourable for clinical implementation in imaging facilities lacking a cyclotron. The $^{68}Ge/^{68}Ga$ generator can be used for 1–2 years and the equilibrium between $^{68}Ga$ and $^{68}Ge$ is re-attained rapidly enough to allow multiple radiotracer preparations daily. Additionally, the $t_{1/2}$ of $^{68}Ga$ is long enough to permit multi-step syntheses and, for the appropriate tracer, data acquisition over longer periods. Therefore, cameras with the highest possible sensitivity are not a prerequisite for obtaining good images. The $\beta^{+}$ range of $^{68}Ga$ does not impair spatial resolution by more than 2.4 mm, the fraction of additional $\gamma$'s is low (3%) and its short $t_{1/2}$ implies a comparatively low radiation dose. With properly designed tracers, $^{68}Ga$ could be as useful for PET as technetium-99m is for SPET.

Injection of $^{68}Ga^{3+}$ in the uncomplexed ionic form results in its very rapid association to native transferrin. The highly stable binding requires that all radiopharmaceutical preparations be free from $^{68}Ga^{3+}$ impurities to ensure that the background blood radioactivity is as low as possible. In vivo formation of $^{68}Ga$-transferrin has been utilised for measuring pulmonary vascular permeability in animals as well as in patients [102–104]. The estimated transcapillary escape rates could be correlated to the progression of the lung disease. $^{68}Ga^{3+}$ has been used to label separated red blood cells for obtaining blood pool images [105] and platelets for detecting induced carotid artery injury, thrombosis or atherosclerosis, particularly if very high resolution cameras are available [105, 106].

Human serum albumin (HSA), macroaggregated HSA (MAA) and albumin microspheres (SAM) have been labelled with $^{68}Ga^{3+}$ [107–113]. These $^{68}Ga$-labelled proteins have been used in PET studies of regional myocardial and pulmonary flow [111, 114–116]. $^{68}Ga$-SAM has served as a standard when validating freely diffusible perfusion tracers since microspheres are mechanically trapped by capillaries and arterioles [117]. When appropriately labelled, they may be used to obtain a highly accurate determination of tissue blood flow.

A number of lipid-soluble $^{68}Ga^{3+}$ complexes have been developed for imaging the brain and heart (see references in [118, 119]). High heart-to-blood ratios and uptakes proportional to blood flow have yielded good-quality PET images, particularly with some of the more recent agents [120–122]; however, high liver uptake of these agents can affect images of the inferior wall of the heart. Most of these compounds are neither freely diffusible nor retained like microspheres, which limits their usefulness in quantifying regional myocardial perfusion. One exception seems to be $^{68}Ga[(4,6\text{-}MeO_2sal)_2BAPEN]^{+}$, which is not cleared during a 90-min observation period [121]. It provides myocardial images very similar to those obtained using [$^{15}O$]water. Modifying the complex so that the tracer clears more rapidly from the blood pool could make this class of compounds very attractive agents for myocardial studies.

Many of the complexes of $^{68}Ga^{3+}$ presented show little brain uptake, indicating that lipid solubility is not the sole requirement for penetration of the BBB [118]. In fact this non-diffusibility has been utilised in clinical studies: $^{68}Ga$-EDTA has improved sensitivity in detecting disruptures of the BBB in brain infarcts, intracranial tumours and multiple sclerosis [123–127] but not in subarachnoid haemorrhage [128].

The hepatic binding protein has been targeted with $^{68}Ga$-deferoxamine-galactosyl-neoglycoalbumin (DF-NGA), a PET correlate to $^{99m}Tc$-NGA [129]. The high tissue specificity indicates that $^{68}Ga$-DF-NGA could be a good agent for studying hepatic function and chronic liver disease. Low-density lipoproteins (LDLs) have been DTPA-chelated with $^{68}Ga^{3+}$ instead of labelled with $^{123}I$ so that lipoprotein catabolism in tissues might be quantified by use of PET [130]. Renal function has been studied in normal subjects with $^{68}Ga$-EDTA [131]. $^{68}Ga$-alizarin (1,2-dihydroxyanthraquinone) has been reported to be a good liver-RES imaging agent and $^{68}Ga$-alizarin red S localises in the renal parenchyma similarly to $^{99m}Tc$-DMSA, allowing imaging of anatomical defects as well as measurement of renal blood flows [132]. $^{68}Ga$-EDTMP and $^{68}Ga$-DTPMP, which combine the bone-seeking characteristics of phosphonic acid and the complexing ability of EDTA and DTPA, have been investigated as skeletal imaging agents [133].

$^{68}Ga$-[DFO]-octreotide was developed for the diagnosis of somatostatin-receptor positive tumours (gastrointestinal, pancreatic, breast and small cell pulmonary tumours) [134]. The $^{68}Ga$-labelled tracer provides a PET complement to the $\gamma$-emitting $^{123}I$-, $^{111}In$- and $^{67}Ga$-octreotides already used in SPET or gamma camera scintigraphy, allowing uptake to be quantified over time. Octreotide is more selective for these tumours than metabolic tracers such as [$^{18}F$]FDG and [$^{11}C$]methionine and it clears from the blood pool and accumulates more rapidly in the tumour than monoclonal antibodies without risking an induced immune response.

Fragments $F(ab')_2$ of a mouse monoclonal antibody for human parathyroid surface antigen, BB5-G1, were labelled with $^{68}Ga$ [135]. Compared to the $^{125}I$-labelled fragments the metal radioactivity cleared much more slowly from the kidney. The labelled fractions appear to be promising PET tracers since high target uptake rela-

tive to muscle was observed in mice implanted with human parathyroid tissue.

$^{68}Ga^{3+}$ is usually obtained from a $^{68}Ge/^{68}Ga$ generator, which is often available on site for routine calibrations and transmission scans. The $^{68}Ga^{3+}$ generator has progressed from the initial solvent extractions [136] to the first chromatographic separation from aluminium with EDTA [137] and finally to the most widely used elution from a tin dioxide support with HCl [138] (see review in [139] and alternative methods in [140–142]). $^{68}Ge$ can be produced by the α-particle bombardment of zinc targets or by proton spallation (600 MeV) of KBr targets. Production routes available using low-energy medical cyclotrons give low yields.

### *Copper*

A number of radionuclides of copper are potentially interesting for nuclear medicine applications: the $\beta^+$-emitters $^{60}Cu$, $^{61}Cu$, $^{62}Cu$ and $^{64}Cu$ with $t_{1/2}$=24 min, 3.4 h, 9.7 min and 12.7 h, respectively, as well as the γ-emitter $^{67}Cu$ with $t_{1/2}$=59 h. Although this range of lifetimes and emission properties offers an unusual flexibility with respect to accessibility as well as potential areas for application, primarily $^{62}Cu$ and $^{64}Cu$ have been utilised thus far. The radionuclide has been complexed to an appropriate carrier for distribution studies or the metal ion alone has been used to study defects in the transport and absorption of copper.

#### Copper-62

$^{62}Cu$ decays almost exclusively by $\beta^+$-emission (97%, $E_{\beta+max}$=2.93 MeV). Interference from other γ's does not have to be considered. Its 9.7-min half-life permits data acquisition with less sensitive PET cameras over longer times for good counting statistics, but is short enough for sequential measurements in a subject to be made in one examination period. These properties are well suited for perfusion agents, which has been the primary area for the application of $^{62}Cu$. Since $^{62}Cu$ can be obtained from $^{62}Zn/^{62}Cu$ generator systems [143, 144], a centralised cyclotron supplier would enable satellite imaging centres to perform planned sequential PET measurements for clinical and/or research purposes. The main disadvantage of $^{62}Cu$ is its high $\beta^+$ energy giving an estimated blur in spatial resolution of 4 mm, which could limit its ability to detect small areas of changes.

Imaging methods based on $^{62}Cu$ have primarily used one well-evaluated multi-organ perfusion tracer, its complex with pyruvaldehyde bis(N4-methylthiosemicarbazone), PTSM [145–148]. $^{62}Cu$-PTSM is a lipophilic, small molecular weight (308 Da) complex which clears rapidly from the blood pool, with high first-pass extraction and prolonged tissue retention. The high initial uptake is due to the diffusion of the complex through the cell membrane (the octanol/water partition coefficient is 100/1 [145]). The mechanism of retention is proposed to be due to the reduction of copper (II) to copper (I) by intracellular sulph-hydryl groups, possibly initiated by the mitochondrial enzymatic system. The latter subsequently binds non-specifically to intracellular macromolecules [149–151].

$^{62}Cu$-PTSM has been used in animals and humans to estimate perfusion [152], primarily in the heart and brain but also in the kidneys and in tumours. Pilot studies in isolated perfused rabbit hearts [153] indicated that its single-pass extraction was ≥40% and its retention invariant for normal physiological flow, hyperaemia, ischaemia and hypoxia. Binding of $^{62}Cu$-PTSM to HSA has, however, recently been shown to make the quantification of hyperaemic flows difficult [154]. PET images obtained are of good quality and are comparable to those obtained using $[^{15}O]H_2O$ [147], although imaging of the inferior wall of the heart is hindered by the considerable uptake in the liver [155, 156]. Pharmacological vasodilation with adenosine revealed that the tracer uptake is diffusion-limited and high flow rates can therefore be underestimated [157]. A mathematical approach for decoupling flow estimates from extraction has been presented and validated [158]. The reduction of copper (II) to copper (I) does not occur immediately and there is some back-diffusion of the tracer during the first 3 min [159], which causes an underestimation of CBF in high-flow regions. $^{62}Cu$-PTSM is rapidly metabolised in vivo. All the radioactivity in the blood 1 min after tracer administration is labelled metabolites [160]. For quantifications requiring the use of an arterial input function, the arterial blood has been subjected to an octanol extraction procedure [158, 161] or a standard curve of average extractions from reference studies has been applied [162].

Albumin has been labelled with $^{62}Cu$ for use as a blood pool agent. Such $^{62}Cu$-labelled tracers are potentially useful for detecting vascular structures, for correcting for radioactivity deriving from the vascular space, and even for assessment of ventricular function. The $^{62}Cu$-labelled agents provide short-lived alternatives to generator-produced $^{68}Ga$-transferrin, which may be a practical consideration when using multi-injection protocols in imaging units lacking an in-house cyclotron. Myocardial images with $^{62}Cu$-benzyl-TETA-HSA (also abbreviated as HSA-2IT-BAT) were found to be identical to the blood volume images obtained using $C^{15}O$ [163]. Data acquisition over longer periods with the longer-lived $^{62}Cu$-labelled tracer can improve image quality. $^{62}Cu$-HSA-DTS has also been successfully used for measuring plasma volume and estimating regional cerebral haematocrit in normal subjects and in patients with cerebrovascular disease [164].

$^{62}Cu$ is eluted from a $^{62}Zn/^{62}Cu$ generator, with preparation of the radiopharmaceutical requiring from less than 1 min to ≈10 min [143, 144, 165–171]. The zinc-62 (half-life 9.26 h) is produced by the nuclear reaction $^{63}Cu(p,n)^{62}Zn$ with a proton beam of 27.5 MeV. The

physical characteristics of the parent nuclide fit well with an on-demand production of the $^{62}Zn/^{62}Cu$ generator by either an in-house or a regional medium-energy cyclotron. The generator can be used for 1–2 days following its production. The production of $^{62}Zn$ as a co-product after the bombardment of a target for the synthesis of $^{123}I$ has also been suggested [172].

## Copper-64

$^{64}Cu$ ($t_{1/2}$=12.7 h) decays by $\beta^+$ emission (18%, $E_{\beta+max}$=0.66 MeV) as well as by electron capture and $\beta^-$ emission. Many of the validation studies of Cu-PTSM during the development of the short-lived $^{62}Cu$ tracer were performed in animals with the long-lived $^{64}Cu$ [155, 160, 173]. The longer half-life is much more feasible for labelling biomolecules (see for example [174–179]). Ionic $^{64}Cu$ has also been used in studies of copper metabolic disorders.

$^{64}Cu$-labelled antibodies are potentially important for estimating radiation dosimetry by using PET to image the tumours prior to therapy with the corresponding $^{67}Cu$-labelled antibody [180]. In high doses, the $^{64}Cu$-labelled antibody might itself be used for radioimmunotherapy. An anticolorectal carcinoma monoclonal antibody, 1A3, and its fragments 1A3-F(ab′)$_2$ have been labelled with $^{64}Cu$ using the bifunctional chelate Br-benzyl-TETA [175]. Tumour uptake in the hamster model was superior to the corresponding indium-111 and iodine-125 labelled antibodies and fragments. $^{64}Cu$-benzyl-TETA-1A3 has shown promise in the detection of small colorectal tumours in humans [181]. High uptake in the kidneys hindered the use of the fragments clinically until a lower molecular weight impurity was removed chromatographically [182]. Both the tumour uptake and the kidney clearance were improved, thereby allowing the fragments to be administered clinically with reasonable absorbed doses. $^{64}Cu$-CPTA-D-Phe-octreotide was synthesised for imaging somatostatin receptors in tumours [183]. Although its uptake in target was 2.5 times higher than that of $^{111}In$-DPTA-D-Phe-octreotide, the high liver and kidney retention made it less desirable for use in humans.

The availability of $^{64}Cu$ provides a means of studying copper transport phenomena in isolated cultures or directly in the organism. Three diseases are clearly attributable to defects in copper metabolism in human cells: Menkes' syndrome, Wilson's disease (WD) and X-linked cutis laxa. $^{64}Cu$ was used to study changes in the uptake and binding affinity for Cu in liver metallothioneins and cells from patients with Menkes' syndrome [184–187]. $^{64}Cu$ export from liver was studied in neonatal pigs as an animal model for patients with WD [188]. In WD patients an increase in urinary copper loss was detected [189], which could have implications for predictions of their response to copper chelation therapy. $^{64}Cu$ has also been used to investigate liver disturbances in copper metabolism in mice bearing ascitic Krebs tumour cells [190] as well as copper excretory capacities in sheep [191].

$^{64}Cu$ can be produced by the proton irradiation of $^{nat}Ni$ [192] or enriched $^{68}Zn$ [193]. Both methods are low-yield routes and suffer from co-production of $^{61}Cu$ and $^{67}Cu$ impurities, respectively. Production in a nuclear reactor by $^{63}Cu(n,\gamma)^{64}Cu$ gives a low specific activity product which may be improved by using the Szilard-Chalmers process [194] or the $^{64}Zn(n,p)^{64}Cu$ reaction. Deuteron irradiation of $^{nat}Zn$ has also been proposed, although the yields are low [195]. Enriched targets have been used for good yields with 19→15 MeV deuterons in the $^{64}Ni(d,2n)^{64}Cu$ reaction [196] or 12→9 MeV proton irradiations in $^{64}Ni(p,n)^{64}Cu$ [197]. The latter method allows the use of low-energy cyclotrons.

## Copper-61

$^{61}Cu$ has physical properties ($t_{1/2}$=3.41 h, $E_{\beta+max}$=1.2 MeV, 61% $\beta^+$ yield) that make it potentially very interesting for in vivo applications. However, to date it has not been utilised to the same extent as either $^{62}Cu$ or $^{64}Cu$. $^{61}Cu$ can be produced by $^{nat}Ni(\alpha,p)^{61}Cu$ (21 MeV) [198] and $^{59}Co(\alpha,2n)^{61}Cu$ (40 MeV), the latter method being free from $^{64}Cu$ impurity [199], as well as by $^{61}Ni(p,n)^{61}Cu$ (12→9 MeV) [197].

### *Technetium-94m*

$^{94m}Tc$ ($t_{1/2}$=52 min) decays by $\beta^+$ emission (70%, $E_{\beta+max}$=2.47 MeV). Access to this radionuclide makes it possible to use PET to solve problems with estimating the uptake of $\gamma$-emitting $^{99m}Tc$-labelled SPET radiopharmaceuticals [200]. The quantitative superiority of PET permits modelling of tracer kinetics, dosimetry measurements and studies of structure-activity relationships with the $^{94m}Tc$-labelled tracers prior to their ultimate wider application in SPET techniques. The successful preparation of $^{94m}Tc$ as pertechnetate allows use of the same commercially available kits to prepare tracers for the PET-operating dual-head cameras which will be chemically identical to those labelled with $^{99m}Tc$, the most important $\gamma$-emitting radionuclide of recent decades.

Perfusion tracers labelled with $^{94m}Tc$ have been used for in vivo myocardial studies. In normal subjects and in patients with perfusion defects, $^{94m}Tc$-teboroxime images were shown to be strongly correlated to those obtained using $[^{13}N]NH_3$ [200]. Good-quality images were obtained even though the increased absorbed radiation dose required that $^{94m}Tc$-teboroxime be administered in doses one-seventh that of $^{99m}Tc$-teboroxime [201, 202]. In a combined SPET/PET study, the extent of defects in patients with coronary disease was found to be similar using PET with $^{94m}Tc$-methoxyisobutylisonitrile (MIBI) and $[^{13}N]NH_3$ but was assessed to be larger with SPET

and $^{99m}$Tc-MIBI [203]. It was suggested that the overestimation could be due to the lack of attenuation correction in SPET.

A number of possible methods for producing $^{94m}$Tc have been examined: $^{94}$Mo(p,n)$^{94m}$Tc (13.5–11 MeV), $^{nat}$Nb($^{3}$He,2n) $^{94m}$Tc (18–10 MeV), $^{92}$Mo(α,pn) $^{94m}$Tc (26–18 MeV) and $^{92}$Mo(α,2n)$^{94}$Ru→$^{94m}$Tc (26–18 MeV) [200, 204–208]. To obtain sufficient yields with small cyclotrons ($E_p$<17 MeV), the $^{94}$Mo(p,n)$^{94m}$Tc is the production method of choice. Using natural molybdenum foil results in six other Tc isotopes as radionuclidic impurities. Methods for avoiding radionuclidic impurities have recently been investigated [209].

*Cobalt-55*

$^{55}$Co ($t_{1/2}$=17.5 h) decays to a large extent (76%) by $\beta^+$ emission. The energy of the $\beta^+_{max}$ is 1.50 (0.58) and 1.04 (0.42) MeV, giving an estimated loss of 1.6 mm in the intrinsic spatial resolution. There are three other γ's (0.48, 0.93 and 1.41 MeV) associated with the decay of $^{55}$Co, resulting in ≈115% extra γ's per $\beta^+$ emission. However, phantom studies with $^{55}$Co have shown that satisfactory resolution can be attained [210] and its pharmacokinetics has been evaluated [211]. Since $^{55}$Co decays to $^{55}$Fe ($t_{1/2}$=2.6 years with an effective dose of about 6 mSv/MBq, ICRP 60) it is important that the relative amounts of the daughter nuclide are not allowed to increase due to long time lapses between production and administration. Even though the build up of activity of $^{55}$Fe would be only a small fraction of that of $^{55}$Co, its contribution to the effective dose might have to be considered.

$^{55}$Co has been used in PET imaging either in the ionic form or chelated with biomolecules. Serial PET studies of pathological processes have been possible up to several days after the tracer administration. $^{55}Co^{2+}$ has primarily been used as a marker for calcium uptake in degenerating brain tissue [212–216] and for quantitative tomocisternography [192]. Intraneuronal accumulation of $Ca^{2+}$ is believed to be a mechanism initiating ischaemia- and disease-related neuronal death [217]. $^{55}Co^{2+}$ normally crosses the intact BBB to a low extent and penetrates the neurones through a non-selective cation entry pathway permeable to $Ca^{2+}$, $Co^{2+}$ and $Mn^{2+}$ [218, 219]. These ion channels are activated to varying degrees by excitatory amino acids [220]. Accumulation of $^{55}Co^{2+}$ in excitotoxic lesions produced by kainic acid in cats illustrated its potential for imaging such neurodegenerative processes [212]. Patients with ischaemic stroke were examined 18–25 h after tracer injection and 20–80 h after the first symptoms [214]. Significant $^{55}Co^{2+}$ accumulation in the damaged area was observed, irrespective of the BBB damage. In some cases this accumulation preceded an anatomical visualisation of the infarcted area by MRI and CT. In patients with moderate traumatic brain injury, PET imaging with $^{55}Co^{2+}$ showed the site and size of the brain damage and also confirmed and localised the EEG findings [216]. The ability to image considerably later than the tracer administration may be a requirement in patients being treated for primary cerebrovascular injury.

$^{55}$Co has been chelated to bleomycin for studies of lung cancer and brain metastases [221–224]. Quantitative information on the biodistribution of $^{55}$Co-labelled monoclonal antibodies in mice has been reported: $^{55}Co^{2+}$ conjugated by 4-ICE to MAbs of human LS-174T tumours showed a tumour uptake higher than that in the blood, liver and kidney [210].

$^{55}$Co production by the $^{3}$He bombardment of Mn has been examined [225]. $^{55}$Co has been produced by the $^{56}$Fe(p,2n)$^{55}$Co reaction using 40→27 MeV protons [226]. The long-lived $^{56}$Co is co-produced, which requires that $^{55}$Co be used within 48 h after bombardment to minimise impurity levels to <5%. The $^{56}$Co impurity is reduced when lower beam energies are used [210]. Alternatively, use of enriched target material in the $^{54}$Fe(d,n)$^{55}$Co reaction is reported to give good yields and purity and the target material can be recovered [227].

*Potassium-38*

$^{38}$K decays with the emission of a positron (100%, $E_{\beta+max}$=2.60 MeV). The half-life ($t_{1/2}$=7.6 min) is short enough to allow test-retest studies, but also long enough to allow data acquisition for several minutes to study organ uptake as well as clearance. Its $\beta^+$ energy causes an estimated 3.5 mm loss in spatial resolution. Phantom studies have shown that quantitatively satisfactory images can be obtained [228]. PET imaging has focussed on cationic $^{38}$K, primarily as a tracer of myocardial perfusion. The whole-body radiation exposure is not a particularly limiting consideration [229, 230]. Since $^{38}$K is fairly short-lived and not generator-produced, only imaging units in close proximity to the cyclotron supplier could feasibly use this nuclide routinely.

$K^+$ is the main intracellular cation. Its transport inside the membrane of the myocardial cell, mediated by the $Na^+/K^+$-ATPase pump, is proportional to regional blood flow and to cell metabolism. Initial extraction is high (85%) [231]. $^{38}K^+$ clears rapidly from the blood and plateaus in the myocardium between 10 and 15 min [156]. Estimates of absolute myocardial perfusion made with $^{38}K^+$ correlated well with those of microspheres, but were less accurate than with [$^{15}$O]$H_2O$ [232]. Similar to $^{82}Rb^+$, its retention is not linearly related to myocardial blood flow at high flow rates and underestimation of flow is unavoidable [156, 233]. Compared with $^{62}$Cu-PTSM and $^{82}Rb^+$, the uptake of $^{38}K^+$ in the liver is low, which is particularly advantageous for studies of the inferior left ventricular wall [156]. Nor does it accumulate in the lungs of smokers as does [$^{13}$N]$NH_3$ [233]. Uptake of $^{38}K^+$ in the stomach does not affect the heart images. Significant effects of spinal cord stimulation for relief of

neuralgic pain at rest and after exercise could not be revealed by study of myocardial perfusion with $^{38}K^{+}$ [233]. An increase in myocardial accumulation of $^{38}K^{+}$ concomitant with a decrease in [$^{18}$F]FDG uptake after nifedipine administration in patients with systemic sclerosis was concluded to indicate the beneficial anti-ischaemic effects of nifedipine [234].

The short-term distribution of $^{38}K^{+}$ in the brain of the cat has been investigated [235]. At 15 min, the radioactivity per gram white and grey matter was 0.12% and 0.13% of the injected dose, respectively. The uptake was diffusion-limited. A rapid uptake was followed by a wash-out phase which was correlated to $PaCO_2$.

A number of routes have been used for the production of $^{38}$K: $^{40}$Ca(d,α)$^{38}$K [236, 237], $^{40}$Ar(p,3n)$^{38}$K [238], $^{40}$Ca(γ,xn)$^{38}$K [239], and the $^{35}$Cl(α,n)$^{38}$K reaction [156, 240–244]. In the last-mentioned method the NaCl target is dissolved in sterile water after irradiation and the resulting $^{38}$KCl can be delivered every 30–40 min, which allows a complete rest/stress study in less than 2 h. A small cyclotron can also be used for good yields of $^{38}$K by irradiating enriched argon with 16–12 MeV protons in the $^{38}$Ar(p,n)$^{38}$K reaction [245]. Although the initial costs of the target material are high, little material is lost in the recovery and it can be recycled for repeated irradiations.

*Bromine-75 and -76*

Bromine radionuclides have, in general, complicated decay schemes with some less than optimal physical properties for in vivo imaging. $^{75}$Br is the most attractive of the bromine radionuclides. $^{76}$Br may give high radiation doses and has a very high $\beta^{+}$ energy, which can degrade the spatial resolution by >5 mm. Despite the disadvantages, quite a number of radiolabelled molecules have been synthesised which primarily target neuroreceptor populations. The chemical reactivity and electronegativity of bromine is intermediate between that of the halogens most commonly used for radiolabelling, fluorine and iodine. Since the C–Br bond is stronger than C–I, the radiolabel is expected to be more metabolically stable than with the iodo-compounds. Bromine-75 and -76 can be produced in specific activities high enough for most applications. Radiolabelling under no-carrier-added conditions is comparable in complexity with that of radioiodinations and is often easier than most syntheses with high specific activity radiofluorine (see review in [246]).

Bromine-75

The half-life of $^{75}$Br ($t_{1/2}$=1.62 h) is of the same order of magnitude as that of $^{18}$F. Thus, $^{75}$Br can potentially be used to synthesise positron-emitting bromine analogues to the fluoro- and iodo-compounds used in PET and SPET. It is also a shorter-lived alternative to the positron-emitting $^{76}$Br, which to date has been more extensively used in labelling PET ligands. $^{75}$Br decays with 71% $\beta^{+}$ ($E_{\beta+max}$=1.74 MeV) and a low intrinsic loss of spatial resolution (2.2 mm). The major contributing γ's are from the 286 keV line (92%).

$^{75}$Br has been used to synthesise: bromo-D-glucose analogues as tracers for the glucose transporter and blood flow agents [247, 248]; a brominated 1,4-benzodiazepine ($^{75}$Br-BFB) promoted more as a cerebral blood flow tracer than a receptor mapping agent since the tracer's transport inside neurons was essentially flow dependent [249, 250]; brominated neuroleptics (*p*-bromospiroperidol, bromperidol, brombenperidol) for studies of the dopamine receptor system [251–254] and zimelidine for study of serotonin receptors [255]. Methods have also been presented for brominating aromatic substrates such as α-methyltyrosine, phenylalanine, uracil and cytosine [256].

The production of reasonable quantities of $^{75}$Br requires access to at least a medium-sized cyclotron. Yields sufficient for investigative studies can be obtained from small cyclotron proton or deuteron irradiations of the krypton-78 or selenium-74-enriched targets, respectively [257–259]. Synthetic quantities, however, are obtained by the bombardment of arsenic-75 with helium-3 [260, 261], $^{78}$Kr with deuterons [262] and $^{76}$Se with protons [263, 264]. Possible production of $^{75}$Br via $^{75}$Kr with 90→68 MeV deuterons has been studied [265].

Bromine-76

$^{76}$Br is a relatively long-lived ($t_{1/2}$=16.2 h) radionuclide which emits positrons in 54% of its decays. The long lifetime can be attractive for the study of ligands which equilibrate slowly in vivo. Target areas may be more optimally visualised by scanning at later times when the non-specific uptake has decreased, as long as there are no recirculating metabolites which increasingly contribute to the specific signal. Radiation exposure considerations may, however, restrict the administered activity and therefore the statistical certainty of observations in humans at late times. The energy of the emitted positron is high compared to that of the conventional PET nuclides, which can be an advantage for radiotherapeutic applications, but is a disadvantage for studies demanding high resolution. Many of the publications on $^{76}$Br-labelled tracers have, in fact, noted that $^{75}$Br has more favourable properties for in vivo applications. In spite of the difficulties, $^{76}$Br-labelled ligands have been successfully used in humans for in vivo mapping of central receptor populations. The majority of these ligands have been developed by the Orsay PET group.

*Norepinephrine analogues.* Loc'h et al. [266] described the synthesis and validation of *meta*-bromobenzylguanidine ([$^{76}$Br]MBBG), the brominated correlate to MIBG

(*meta*-iodobenzylguanidine). These compounds are functional analogues of norepinephrine that enter the neuron through the same amine pump [267] and are taken up by myocytes [268]. It can be difficult to quantify the uptake of γ-emitting [$^{131}$I]- and [$^{123}$I]MIBG with SPET, particularly when the enhancement in the target organ is not very large compared to the adjacent tissue. Valette et al. [269] reported that [$^{76}$Br]MBBG had a high cardiac uptake (heart/lung=5–8/1 in dogs) and that its neuronal uptake appeared to be less dependent on passive diffusion than that of [$^{123}$I]MIBG. In PC-12 phaeochromocytoma tumours in nude mice, Clerc et al. [270] reported a high early uptake of [$^{76}$Br]MBBG which peaked after 8 h and an intracellular distribution of radioactivity similar to that of [$^{123}$I]MIBG. The high affinity of [$^{76}$Br]MBBG for the tumour target and the tenfold greater range of the particles emitted indicated promise for use of this tracer to quantify tumour uptake as well as for internal radiotherapy, even at centres located a considerable distance from the cyclotron facilities.

*Dopamine-$D_2$.* [$^{76}$Br]Spiperone (BSP) was one of the first PET ligands shown to localise preferentially in $D_2$-rich areas, and it was also shown that its binding in the striatum of the baboon was saturable and could be displaced by spiperone [271, 272]. Neuroleptic interaction with $D_2$ binding sites was illustrated by the lower [$^{76}$Br]BSP striatum/cerebellum ratios in haloperidol-treated schizophrenics than in a control group [273]. Loss of striatal $D_2$ receptors in a neurological disease (progressive supranuclear palsy) was demonstrated in vivo with PET for the first time with [$^{76}$Br]BSP [274]. [$^{76}$Br]Bromolisuride (Blis) binds more selectively to $D_2$ receptors than BSP and its striatal uptake is 2 times larger [275]. A method for in vivo kinetic analysis using multiple injections of [$^{76}$Br]Blis in baboons has been presented [276]. [$^{76}$Br]Blis revealed the $D_2$ receptor loss in the pharmacologically lesioned striatum and nigral dopamine cells in baboons [277]. A comparison of the striatum/cerebellum ratios of [$^{76}$Br]Blis uptake in schizophrenics with those of a control group corroborated the results obtained with $^{11}$C-ligands indicating no quantifiable differences in the numbers of $D_2$ receptors in schizophrenics [278]. Brominated benzamides FLB 457 and FLB 463, labelled with $^{76}$Br, have been shown in the baboon to bind selectively and with high affinity to $D_2$ receptors [279], and it has been suggested that [$^{76}$Br]FLB 457 may possibly be useful for the study of extrastriatal $D_2$ receptors.

*Dopamine-$D_1$.* The $^{76}$Br-labelled antagonist SCH 23390 has been shown to localise in $D_1$-rich areas in both mice and monkeys [280]. NNC 22-0010, a $D_1$ antagonist labelled with $^{11}$C and $^{76}$Br, showed regional uptake in primates that was consistent with $D_1$ localisation [281]. Possible advantages of the $^{76}$Br-labelled ligand for test-retest reproducibility in binding site quantification and for metabolic studies at times exceeding 1 h were discussed.

*Benzodiazepine.* In a preliminary report [282], the partial agonist NNC 13–8199 was reported to accumulate preferentially in regions with high benzodiazepine receptor density and the binding was readily displaced by flumazenil.

*m-Acetylcholine.* Changes in muscarinic acetylcholine receptors are believed to be associated with the development of neurodegenerative disorders such as dementia. The antagonist [$^{76}$Br]BDEX ($^{76}$Br-4-bromodexetimide) was shown to accumulate preferentially in mAChR-rich areas, i.e. the frontal cortex, hippocampus and striatum, of rats and baboons [283]. The radioactivity in frontal cortex reached a plateau in <0.5 h while that in the cerebellum continued to decline throughout the observation period (5 h). Selective uptake could be prevented by pharmacological challenge.

*Polypeptides.* Mouse epidermal growth factor, as a model for polypeptide distribution studies, was labelled with $^{76}$Br and compared with the corresponding $^{125}$I-labelled polypeptide [284]. Differences in the organ uptake of $^{76}$Br and its binding to high molecular weight plasma components were attributed to differences in metabolic stability and the strengths of the C–halogen bonds.

$^{76}$Br is produced by the $^{3}$He irradiation of thin metallic arsenic or $Cu_3As$ alloy targets [260, 285, 286]. With higher energy beams, the radiopharmaceutical preparation is delayed by 15 h in order to reduce the $^{75}$Br contamination. Highest thick target yields have been reported for the $^{76}$Se(p,n)$^{76}$Br reaction [287, 288] but the high cost of the enriched $^{76}$Se has probably contributed to the fact that it is not used for synthetic batch productions. The $^{nat}$Br(p,xn)$^{76}$Kr→$^{76}$Br reaction (see review in [289, 246]) requires high-energy beams and suffers from the rather large impurity of $^{77}$Br. Separation techniques have, however, been examined to optimise the yields of isolated $^{76}$Br [290].

### *Iodine-124*

$^{124}$I has a complex decay scheme. Only 23% of its decays lead to the emission of positrons, most of which are of relatively high energy. Many high energy γ's are also emitted (>200% per $\beta^+$ decay), some in cascade with the positrons. The spatial resolution of PET images with $^{124}$I-labelled ligands is comparable to that of images with the traditional PET radionuclides: estimated loss in spatial resolution is 2.3 mm. However, image quality can be enhanced somewhat if the ligand is highly specific for the target, if the imaging time is prolonged and if, when feasible, the administered activity is increased [291, 292]. The long half-life (4.2 days) can allow serial scanning of slow physiological processes over a period of days. For ligands with long biological half-lives, the radiation dose may be a severe limiting factor. Obviously its use does not require proximity to the accelerator.

Most of the applications published have used $^{124}$I supplied by the King Faisal Specialist Hospital in Riyadh, Saudi Arabia.

When the PET images are satisfactory, $^{124}$I can be an attractive complement to γ-emitting iodine nuclides for predicting dosimetry for therapy with $^{131}$I-labelled agents and for improving the accuracy of organ volume determination. Differentiated [$^{124}$I]NaI uptake was reported in multinodal goitres of patients scheduled for partial thyroidectomy or radioiodine treatment [293]. The volumes estimated by $^{124}$I/PET agreed well with those measured following surgery. Functioning thyroid volume was assessed with an accuracy of ±4%–14% using $^{124}$I [294]. Flower and collaborators [295] performed [$^{124}$I]NaI PET scans of patients with Graves' disease. Reliable images as well as accurate calculations of uptake and estimations of dose delivery were obtained, which led to changes in their protocol for therapy with [$^{131}$I]NaI. The concentrations of [$^{124}$I]MIBG in tumour sites in the lung, liver and abdomen of patients with neuroblastoma and phaeochromcytoma were more reliably estimated with PET than with SPET/[$^{123}$I]MIBG [296].

The long half-life of $^{124}$I is particularly suited for in vivo studies of the prolonged time course of uptake of monoclonal antibodies (MAbs) in solid tumours. The radiation dose delivered for the $^{124}$I-labelled MAbs will depend on the organ and the antibody used but is typically 0.5–2.5 times the corresponding $^{131}$I dose [297]. Higher doses have therefore been allowed in diagnostic studies of patients already scheduled for radiotherapy. The uptake of $^{124}$I-labelled 3F8 MAb has been investigated in neuroblastoma-bearing rats, a child with neuroblastoma and a patient with glioma [291, 298, 299]. In the rat studies there was a good agreement between the $^{124}$I images and biodistribution determined by excision. Variation with time of the uptake of the antibody could be assessed. Binding constants for the labelled antibody and the dosimetry for [$^{131}$I]3F8 radiotherapy could be estimated. ICR 12, a MAb specific for the human c-*erb*B2 proto-oncogene product, was successfully labelled with $^{124}$I and imaged in mice bearing human breast carcinoma xenografts [300]. Rubin and collaborators [301] reported the specific tumour localisation of $^{124}$I-labelled MAbs MX35 or MH99 in rats with subcutaneous human ovarian cancer xenografts. Miraldi and collaborators [302] utilised the 4% impurity of $^{124}$I in commercially available $^{123}$I to perform a double labelling of 3F8 and subsequently show that the PET images were more detailed but otherwise corresponded well with the planar images.

[$^{124}$I]Iodo-α-methyltyrosine was used to validate the corresponding $^{123}$I-labelled compound for SPET [303]. Specific uptake was observed in glioblastomas and the tumour/cortex ratios changed only minimally between 15 and 60 min. It appears that its uptake can be used as a measure of amino acid transport, but not of incorporation into protein.

$^{124}$I can be produced using a low- to middle-energy proton machine and the $^{124}$Te(p,xn)$^{124}$I reaction [304–306]. The $^{124}$Te(d,2n)$^{124}$I process, which has been used in Riyadh for world-wide deliveries, is described in [307, 308]. Methods for recovering 99% of the $^{124}$Te from various target materials have been presented [309]. Enriched $^{125}$Te costs less than $^{124}$Te. Yields for $^{125}$Te(d,3n)$^{124}$I are reported to be lower [309] but acceptable with the $^{125}$Te(p,2n)$^{124}$I reaction [310]. In the latter method, $^{123}$I (8%) would reduce by decay during isolation and transport while $^{125}$I was of the order of 5%. Quality control of $^{124}$I has been presented in [311].

### *Yttrium-86*

$^{86}$Y ($t_{1/2}$=14.7 h, $\beta^+$=33%, several positrons with $E_{\beta+max}$ varying from 2.34 MeV (4.6%) to 1.04 MeV (15%) and >600% γ's per $\beta^+$ emission) is interesting primarily for the possibility of using PET to quantitatively assess the pharmacokinetics of $^{90}$Y agents used in the palliative treatment of painful bone metastases. Since $^{90}$Y decays entirely by $\beta^-$ emission, a corresponding γ- or $\beta^+$-emitter ($^{87}$Y or $^{88}$Y vs $^{86}$Y) is needed for estimating optimal therapeutic doses for humans. The half-life of $^{86}$Y is long enough for sequential scans over several days. The localisation of $^{86}$Y-citrate in a patient with disseminated bone metastases from breast cancer was studied for up to 45 h using PET [312]. Assuming constant storage of yttrium in the metastases and skeleton and using the uptake kinetics of the $^{86}$Y agent, radiation doses to the individual metastases and normal tissue (bone, liver, red marrow) for the $^{90}$Y agent could be calculated. The biodistribution of $^{86}$Y-citrate was compared with that of $^{86}$Y-EDTMP in patients with prostatic cancer and multiple bone metastases [313]. Both agents showed high tumour to bone uptake (average ≈8), but their kinetics differed. Maximum uptake was reached faster with the EDTMP complex (1.5 h vs 2 days), but $^{90}$Y-citrate was predicted to give higher doses to the metastases.

$^{86}$Y can be produced either by bombarding $^{86}SrCO_3$ with 14.2→10.2 MeV protons in the $^{86}$Sr(p,n)$^{86}$Y reaction or $^{nat}Rb_2CO_3$ with 24→12 MeV $^3$He in the $^{nat}$Rb($^3$He,2n)$^{86}$Y reaction [314]. The former gives fewer radioactive impurities (4% vs 300%) and can be performed using small cyclotrons. The enriched target can be recovered with good yields (90%).

### *Miscellaneous*

#### Chlorine-34m

$^{34m}$Cl [$t_{1/2}$=32 min, $\beta^+$=54%, $E_{\beta+max}$=2.47 MeV (0.57) and 1.35 MeV (0.43)] is potentially interesting since it is intermediate in size and electronegativity between the $\beta^+$-emitter $^{18}$F and the γ-emitter $^{123}$I. It can be considered an isostere of oxygen or hydroxyl substituents, which can generate new routes to $\beta^+$-emitting analogues of O-containing compounds. However, it has a complicated

decay scheme with $\beta^+$ contributions from $^{34}$Cl, which impairs the spatial resolution. $^{34m}$Cl can be produced by $^{34}$S(p,n)$^{34m}$Cl at 22 MeV [315] and $^{35}$Cl(p,x)$^{34m}$Cl at 35→22 MeV [316].

### Zirconium-89

Due to its long half-life, $^{89}$Zr ($t_{1/2}$=3.27 days, $\beta^+$=23%, EC=77%, $E_{\beta+max}$=0.897 MeV) has been suggested for use in quantifying the deposition of monoclonal antibodies in tissue or tumour [317]. The Zr-Desferal complex has been reported to be highly stable with <0.2% of the Zr lost in 24 h [318]. Using the long-lived $^{88}$Zr-Desferal in a preliminary report [319], the antibody 323A3 was successfully labelled. $^{89}$Zr can be obtained by the reactions $^{89}$Y(p,n)$^{89}$Zr and $^{89}$Y(d,2n)$^{89}$Zr [317–321].

### Strontium-83

Palliative therapy with $^{89}$Sr has been extensively used for pain in disseminated bone metastases. Use of the $\beta^+$-emitter $^{83}$Sr [$t_{1/2}$=1.35 days, $\beta^+$=24%, $E_{\beta+max}$=1.23 MeV (0.90) and 0.803 MeV (0.10)] and PET has been proposed as a means of estimating strontium uptake in individual metastases and other tissues and to optimise therapy. PET phantom measurements have been performed for evaluation of $^{89}$Sr dosimetry [322]. $^{83}$Sr has been produced by $^{82}$Kr($^3$He,2n)$^{83}$Sr with 18→10 MeV [322] with radioactive impurities of 1% and 2.5%, respectively. The daughter $^{83}$Rb should be considered when calculating radiation doses due to its long half-life and its emission of several intense $\gamma$'s.

### Manganese-51 and -52

$^{51}$Mn ($t_{1/2}$=46.2 min, $\beta^+$=97%, $E_{\beta+max}$=2.21 MeV) and $^{52}$Mn ($t_{1/2}$=5.6 days, $\beta^+$=29%, $E_{\beta+max}$=0.575 MeV) have been suggested for use in the diagnosis and treatment of blood diseases [323], as cationic perfusion tracers [324] and for the study of the involvement of manganese in the pathophysiology of degenerative neurological diseases [325]. $^{51}$Mn decays with formation of a daughter $^{51}$Cr which has a $t_{1/2}$ of 28 days, requiring that biodistribution of the daughter nuclide be charted and accounted for in dosimetry calculations. $^{52}$Mn, on the other hand, decays to a stable nuclide, but >1000% $\gamma$'s are emitted per $\beta^+$ emission and may account for high radiation doses. Both radionuclides have been produced in acceptable yields on small cyclotrons by $^{54}$Fe(p,$\alpha$)$^{51}$Mn and $^{52}$Cr(p,n)$^{52}$Mn reactions using 16.2 MeV protons [325] or on larger machines by the $^{51}$V($^3$He,2n)$^{52}$Mn reaction [323].

### Iron-52 and manganese-52m

$^{52}$Fe ($t_{1/2}$=8.28 h, $\beta^+$=56%, $E_{\beta+max}$=0.804 MeV) and $^{52m}$Mn ($t_{1/2}$=21.1 min, $\beta^+$=97%, $E_{\beta+max}$=2.63 MeV) have been proposed as bone marrow tracers [326–328] and for myocardial imaging, respectively [324, 329]. $^{52m}$Mn is generator produced in the decay of $^{52}$Fe [330, 331]. $^{52}$Fe can be produced by $^{52}$Cr($^3$He,3n)$^{52}$Fe [332], $^{50}$Cr($^4$He,2n)$^{52}$Fe [333], $^{55}$Mn(p,4n)$^{52}$Fe [334, 335] and $^{nat}$Ni(p,x)$^{52}$Fe [335, 336]. Such a generator must, however, be replenished frequently since the mother nuclide is so short-lived.

### Indium-110

Indium isotopes are routinely used to label biomedical molecules, particularly blood components, for diagnostic studies. At present the SPET nuclide $^{111}$In ($t_{1/2}$=67 h) is the most widely used. The $\beta^+$-emitter $^{110}$In ($t_{1/2}$=1.15 h, $\beta^+$=62%, $E_{\beta+max}$=2.25 MeV) would allow analogous compounds to be quantified with PET and sequential studies to be performed within a relatively short time. Production methods that have been proposed are $^{110}$Cd(p,n)$^{110}$In [337] and the generator systems In(p,xn)$^{110}$Sn→$^{110}$In [338] and $^{110}$Cd($^3$He,3n)$^{110}$Sn→$^{110}$In [339]. The irradiation using enriched $^{110}$Cd can be accomplished with high production yields using a small cyclotron (<13 MeV) and the target material can be recovered. Similar to the $^{52}$Fe/$^{52m}$Mn generator, since decay to $^{110}$In occurs with a $t_{1/2}$=4.11 h, the generator will have to be replenished regularly from a larger host accelerator with 70 MeV protons or 36 MeV $^3$He.

### Iodine-120

$^{120}$I [$\beta^+$=46%, $t_{1/2}$=1.35 h, with a number of positrons with $E_{\beta+}$ ranging from 1.5 MeV (4.8%) to 4.6 MeV (42%)] has been suggested as an alternative to $^{124}$I for applications in which shorter $t_{1/2}$ and higher $\beta^+$ emission are required [340]. The nuclide has a physical half-life compatible with the kinetics of MIBG, which is commonly labelled with $^{123}$I for somatostatin receptor studies, and the absorbed dose for $^{120}$I-MIBG has been estimated [341]. $^{120}$I is produced by the reaction $^{122}$Te(p,3n)$^{120}$I using 35 MeV protons with a yield of 7 mCi/$\mu$Ah [340]. General drawbacks to its use are the large loss in spatial resolution (5.4 mm) and >600% $\gamma$'s per $\beta^+$ emission.

### Iodine-122

Labelling of highly extracted compounds with $^{122}$I ($\beta^+$=77%, $t_{1/2}$=3.6 min, $E_{\beta+max}$=3.1 MeV) has been used as a route to sequential rCBF measurements. 2,4-Dimethoxy-*N*,*N*-dimethyl-5-[$^{122}$I]iodophenyl-isopropylamine and

[$^{122}$I]-iodoperidol, analogues of amphetamine and haloperidol, respectively, have been synthesised for perfusion studies [342, 343]. Rapid electrophilic labelling techniques typically used with other iodine radionuclides gave purified product in ≤5 min. In animal studies, both tracers were rapidly extracted and retained in cerebral tissue. Since radio-deiodination is not as much a concern with this very short-lived nuclide, other analogues which have been shown to be metabolically unstable might be usable in these short scanning times. $^{122}$I is generator produced from $^{122}$Xe gas, which is a by-product of the $^{127}$I(p,5n)$^{123}$Xe production of high-purity $^{123}$I [342]. The half-life of $^{122}$Xe (20.1 h) makes it necessary to replace the generator 2–3 times a week, depending on the work load.

### Arsenic-72

$^{72}$As [$\beta^+$=88%, $t_{1/2}$=1.08 days, $E_{\beta+max}$=3.32 MeV (0.20) and 2.49 MeV (0.80)] has been suggested for in vivo use as a chemical analogue of phosphorus. It can be produced by $^{72}$Ge(p,n)$^{72}$As using 14 MeV protons and the enriched target material can be recovered by dry distillation [344]. A drawback is the high radiation dose, which will restrict the administered activity at long biological half-lives.

### Antimony 118

$^{118}$Sb ($\beta^+$=74%, $t_{1/2}$=3.5 min, $E_{\beta+max}$=2.7 MeV) for potential use in the cationic or complexed form is generator produced from the longer-lived tellurium-118 ($t_{1/2}$=6 days) obtained by bombarding $^{nat}$Sb targets with 67.5→25 MeV protons [345, 346]. $^{118}$Sb gives low radiation doses and has no serious physical drawbacks other than the short half-life of the parent, requiring scheduling for its frequent replacement.

## Summary

The positron-emitting radionuclides span a wide range of half-lives and physical properties. Thus, in principle, it would appear that an appropriate radionuclide could be found to suit most clinical demands. In practice, however, the applicability of a radionuclide is very much dependent on how and in what quantities it can be produced, whether and how far it can be transported, whether there are undesirable components in its decay scheme and, if so, how they affect image quality, whether the radionuclide is chemically convertible to radiotracers with appropriate biochemical behaviour and, finally, whether its characteristics are compatible with the clinical questions being asked and the imaging techniques available to study them.

Even though $^{18}$F and the bio-isotopes $^{11}$C, $^{13}$N and $^{15}$O are the most important radionuclides for PET applications, other radionuclides are available that can be transported from a remote cyclotron for imaging with optimised PET cameras, coincidence coupled dual-head cameras or SPET cameras supplied with specially designed collimators and shielding. Several PET radionuclides have a SPET analogue ($^{94m}$Tc/$^{99m}$Tc, $^{124,122,120}$I/$^{123,131}$I, $^{75,76}$Br/$^{77}$Br, $^{110}$In/$^{111}$In). Many molecules of biological interest also contain groups or functionalities that permit alternative labelling routes utilising either PET or SPET radionuclides. Integration of PET and SPET radiotracer development would pave the way for better exploitation of the current strengths of the two techniques. Higher photon detection efficiency and higher spatial resolution are achieved with PET due to the “electronic” collimation in coincidence detection. PET is also quantitatively superior to SPET, although new instrumentation and methods for scatter and attenuation correction in SPET are reducing the differences. On the other hand, SPET and planar scintigraphy have an efficient world-wide net of radionuclide distribution and pre-manufactured radiolabelling kits. Daily labelling procedures are therefore simple, making such nuclear medicine techniques rational in clinical routines. A modern SPET camera system costs between one-third and one-fifth as much as a high-resolution PET camera, which further contributes to its economic feasibility.

In an ideal world, the first criterion for the choice of imaging technique to be used should be the reliability of the information obtained. Once the reliability has been ascertained, then cost-effectiveness demands must be considered. Integration of the imaging techniques would allow kinetic information obtained from PET radiotracer validations to be directly used to optimise tracers for SPET, particularly when the only difference between the tracers is that different isotopes of one of the atoms in the molecule are used. In this way PET methodology could fairly easily be transferred to the more widely available SPET for large population studies or implementation into diagnostic routines. Furthermore, differences in the half-lives of the PET/SPET radionuclide analogues make complementary multi-technique studies feasible in which the time of the in vivo observation could more appropriately be adapted to the speed of the biological process studied. Dual-headed camera systems for SPET and for whole-body imaging have recently become an attractive alternative for high-volume, routine nuclear medicine investigations. When supplied with heavy high-energy collimators with thick septa, these cameras can also be utilised with PET radiopharmaceuticals using conventional single-photon detection. However, both the spatial resolution and the sensitivity of these applications will be greatly improved by the coincidence-coupled dual-head cameras under development.

Most of the radionuclides and generator systems reviewed here can be produced by a medium→high-energy (<40 MeV) cyclotron. In general, the longest-lived nuclides can be transported and used up to day(s) after their production, although it must be remembered that

the fraction of radioactive impurities and/or daughter nuclides may grow as the desired radionuclide decays. Those radionuclides with short half-lives such as $^{38}K$ can only be implemented in proximity to the production site. The generator-produced radionuclides allow a certain amount of self-sufficiency, except for those which must be replenished on a daily basis due to the short half-lives of the mother nuclide [$^{52}Fe/^{52}Mn$ (8.28 h), $^{62}Zn/^{62}Cu$ (9.26 h), $^{110}Sn/^{110}In$ (4.11 h)].

There are further physical factors to be considered which may restrict use of alternative radionuclides in certain clinical situations and/or with certain camera systems. For instance, when high spatial resolution is required, such as in imaging the functional behaviour in small structures within an area with a complex uptake pattern, radionuclides that emit high-energy positrons are not an optimal choice and should probably be avoided. The intrinsic spatial resolution for images using $^{38}K$, $^{62}Cu$, $^{76}Br$, $^{82}Rb$ and $^{120}I$ will be further impaired by 3.5, 4.0, 5.7, 4.7 and 6.3 mm, respectively, due to their high positron energies.

For some applications, a high photon flux may be problematic. The detection rate of random events in dual-head coincidence systems without collimators is very high with $^{18}F$ and may be accentuated when using any of the radionuclides that emit a large fraction of $\gamma$'s per $\beta^+$ emission: for instance, $^{52}Mn$ (1018%), $^{83}Sr$ (313%) and $^{86}Y$ (882%). Some of the radionuclides ($^{38}K$, $^{51}Mn$, $^{52}Fe$, $^{75}Br$ and $^{118}Sb$) have additional $\gamma$'s with very high energies, which would be expected to penetrate through a SPET collimator and head shieldings, thereby limiting their applicability in such systems. However, neither $^{62}Cu$ nor $^{68}Ga$ have $\gamma$'s that restrict their use in either PET or SPET systems.

Finally, some of the alternative radionuclides considered for clinical use in this review ($^{52}Mn$, $^{55}Co$, $^{72}As$, $^{76}Br$ and $^{124}I$) may give high radiation doses, especially at long biological half-lives. The administered radioactivity will have to be reduced accordingly, with image quality degraded by the poor signal to noise ratios.

In spite of the physical limitations summarised here, some of these alternative radionuclides have been quite successfully used in specific research and clinical applications. However, the avenues chosen for applications of such radionuclides will be taken by many more imaging units when the match between physical properties and clinical and imaging limitations is as optimal as possible.

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