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PRODUCTION OF ^{18}F FOR BONE SCANNING

by

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The first application of ^{18}F to biologic work was made in 1940 but the use of the isotope was rendered difficult by the fact that only small activities could be produced (BERNSTEIN & KATZ 1953). It was later observed (KNIGHT, NOVEY, CANON & TURKEVICH 1951) that ^{18}F could be produced in a thermal reactor by the irradiation of a compound containing both lithium and oxygen. Since then the production of quite large activities on an economic basis has been easy.

If no commercial radiochemical processing laboratories are near, ^{18}F may be prepared on the spot provided a thermal reactor with a flux of the order of 10^{12} n/s · cm^2, such as is frequently available in universities and training institutes, lies within 20 km of the clinic. The half-life of only 110 min of ^{18}F may then possess few disadvantages. The practical preparation of ^{18}F in the normal isotope laboratory of a radiotherapy clinic was the aim of this work; the isotope should be in a form suitable for in vivo studies, particularly when it is required for oral administration in bone scanning.

The production of ^{18}F. A number of nuclear reactions result in the production of ^{18}F activity, such as ^{18}O(p,n)^{18}F in cyclotrons and reactors (CARLSON et coll. 1959, NUSYNOWITZ et coll. 1965). In thermal reactors, production can be ef-

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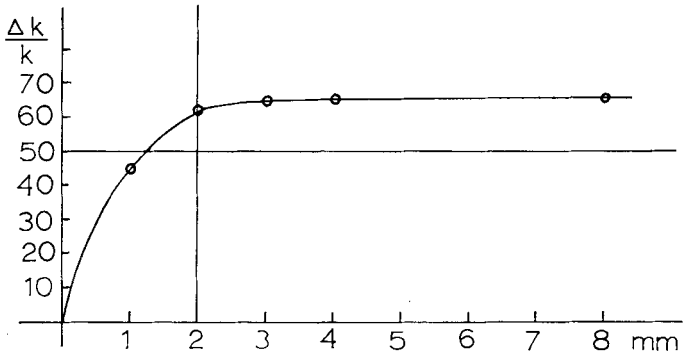

Fig. 1. Effect of thickness of sample on the reactivity of the reactor, and thus on the specific activity of the sample.

fected by a chain reaction, at first $^{6}Li(n, {}^{4}He)\ {}^{3}H$. The resulting fast tritons ^{3}H will induce ^{18}F activity by $^{16}O({}^{3}H,n){}^{18}F$ (BERNSTEIN & KATZ 1953, KNIGHT et coll. 1951). These two reactions are induced simply by setting some lithium salt containing oxygen in the neutron flux of a thermal reactor.

BEG & BROWN (1963) utilised Li_2O for this production. Their method is applicable for medical purposes if a modification is introduced in view of the high tritium content in the product. However, in common with many others, we have made use of Li_2CO_3, irradiated at the Institute of Technology at Otaniemi in a Triga reactor with a maximum power of 100 kW. If the ^{18}F is to be without chemical and radiochemical impurities, the sample needs some chemical purification after irradiation. Known methods of distillation (ERICSSON 1961, THOMAS et coll. 1965) could not be used for the separation of ^{18}F, as at first the simple apparatus required for this purpose was not available. Moreover, the high tritium content associated with this method (THOMAS et coll.) was considered undesirable. Accordingly, with the method first applied we used AlO as an ion exchanger (STANG 1963). This procedure appeared too slow, however, at least with the chromatographic alumina at hand, wherefore the following method was thereafter employed.

Three grams of irradiated Li_2CO_3 (two hours in $4 \cdot 10^{12}$ n/s · cm^2) are first dissolved in 30 ml 2.7 normal HCl. The carbonate is released and therefore the process should be carried out under a fume hood and behind lead bricks to avoid radiation hazards. The dose rate at 20 cm, without shielding, is about 20 mR/hour. One millimole of H_3PO_4 is added together with 0.2 mM of a $CaCl_2$ solution. The pH is adjusted to about 9 (or more) by the addition of 10 ml 2.5 normal NaOH. Calcium phosphate, carrier of the main part of the ^{18}F activity, is

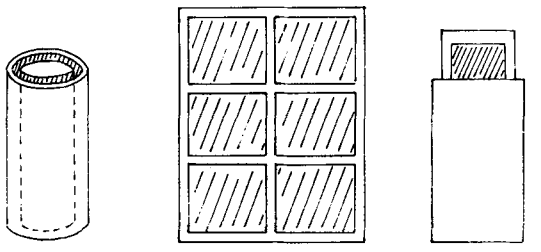

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Fig. 2. Forms of sample packages used in the neutron irradiation. a) Cylindrical sample made of plastics. b) Flat sample made of plastics. c) Sample of aluminium. Shaded areas refer to Li_2CO_3.

then precipitated. The phosphate is filtered off in a glass filter (5 to 15 microns) and washed. Tritium and lithium are thus separated from ^{18}F. The phosphate is dissolved in 5 ml 2.7 normal (warmed) HCl in the filter. Finally, about 10 ml of concentrated Na_3-citrate is added for adjustment of the pH to about 4. The solution is now ready for oral use.

This method differs slightly from the one described by ANBAR (1963).

The final solution usually carries an activity of 1 mCi of ^{18}F per 3 g of irradiated lithium carbonate. From the moment the sample is taken out of the reactor, 6 km from the clinic, one hour has elapsed. Chemical separation by the method described takes about 20 minutes. The yield is usually about 80 %. If the solution is to be used for intravenous injection, it must be neutralized, and no citrate should be added (ANBAR 1963, DWORKIN et coll. 1965, THOMAS et coll. 1965).

Form and size of the sample during neutron irradiation. The size of the lithium carbonate sample greatly influences the specific activity achieved at neutron irradiation, by reason of the large cross-section of ^6Li to thermal neutrons. If the thickness of the sample should exceed 2 mm, the specific activity will no longer rise (Fig. 1). This means that the sample will be effectively irradiated only to a depth of 1 mm from the surface.

The samples used have been either cylindrical (Fig. 2a) or flat (Fig. 2b). The boxes are made of a plastic material, usually a thin plastic foil. An aluminium envelope has also been employed (Fig. 2c). This is however not practical as the aluminium is also activated and is accordingly difficult to handle. Bags made of thin plastic foil seem to be the best choice since they will not be radioactive, are easily cut open, and may be discarded after use. In these packages, the thickness of lithium carbonate will not exceed 2 mm. If enriched lithium (^6Li) is utilised, the cross-section of the carbonate will be more than ten times as large, and therefore the thickness of the lithium carbonate should not exceed 0.2 mm.

Table 1

Activity present in an irradiated sample of 3 g Li_2CO_3

Isotope	Activity	
^{3}H	2 600	μCi
^{18}F	2 000	»
^{24}Na	1.0	»
^{38}Cl	2.0	»
^{36}Cl	0.03	»
^{35}S	0.003	»
^{42}K	0.003	»

Table 2

Radiation dose due to oral administration of 1 mCi ^{18}F at 30 minutes after irradiation with no purification of sample

Isotope	Activity (μCi)	Total body (mrad)	Bone (mrad)
^{3}H	1 600	120	120
^{18}F	1 000	30	230
^{24}Na	0.61	1.0	1.0
^{38}Cl	0.55	0.03	0.03
^{36}Cl	0.018	0.13	0.13
^{35}S	0.002	0.02	0.01
^{42}K	0.002	0.01	0.01
	Total	150 mrad	350 mrad

An increase in thickness entails a loss in the excess amount of the carbonate, without any gain of activity.

Radioactive components of an irradiated Li_2CO_3 sample. After irradiation and before purification, isotopes other than ^{18}F exist in the sample, dependent upon the presence of impurities in the irradiated carbonate. The most important by-product is naturally tritium. Theoretically, there should be about 5 mCi of tritium to 3 g of Li_2CO_3, although in practice much less is obtained (Table 1). This indicates that the geometry of the sample concerned is not the best possible.

Only ^{18}F and ^{24}Na peaks are detectable 24 hours after irradiation in the gamma spectrum of an irradiated sample. ^{38}Cl, which has an initial activity of 2 μCi, has a half life of 37 minutes and thus completely vanishes 24 hours after irradiation (1.60 and 2.15 MeV gammas). ^{42}K has such a slight activity that it is not discernible in the spectrum. ^{3}H, ^{35}S and ^{36}Cl have no gamma transitions.

Radiation dose induced by different isotopes in the sample. The dose to the patient caused by the activities present, when one millicurie of ^{18}F is administered and the sample is not purified, is small (Table 2). Only fluorine and tritium produce an appreciable dose. When tritium and other isotopes are separated from the fluorine, the radiation dose of ^{18}F per 1mCi will be reduced by 35 % in bone and by 80 % in the entire body. In any event, the dose does not seem to be excessive, and for this reason the separation of tritium is not absolutely necessary. The separation of lithium, which is not radioactive, has been considered essential (STANG & RICHARDS 1964). Three grams of lithium carbonate contain 0.57 g

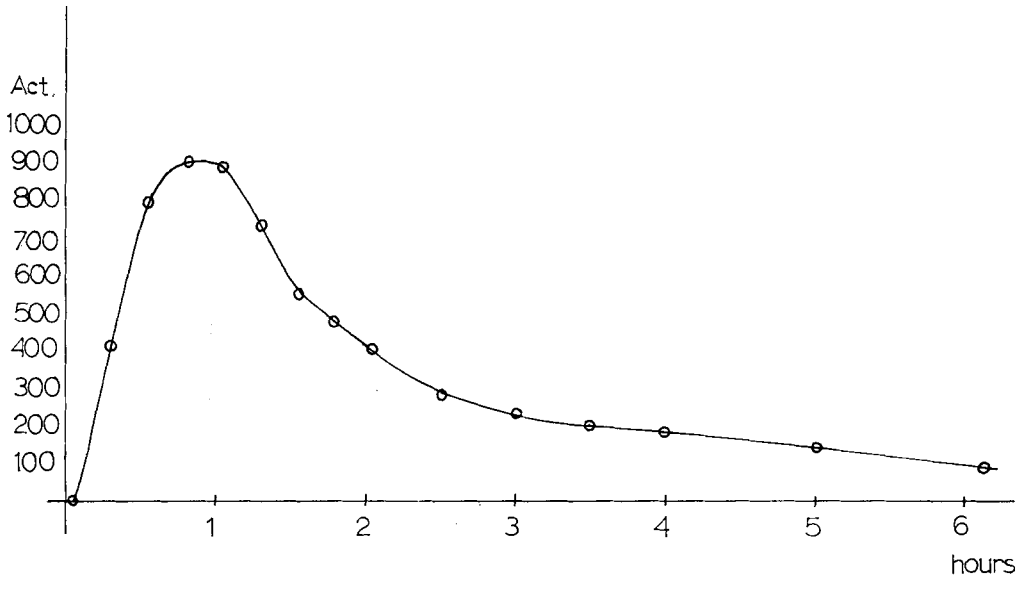

Fig. 3. Blood excretion curve after an oral dose of carrier-free ^{18}F-fluoride.

lithium. It may be assumed that under certain conditions a single dose exerts no toxic effects, but the amount could nevertheless be further reduced by a tenth by the use of isotopically-enriched ^{6}Li-lithium carbonate.

The method of purification outlined above, although not essential, has been applied because it is relatively quick and simple. After purification, only ^{18}F and ^{35}S isotopes are present in the final solution. Measurements have indicated, however, that some contamination with ^{3}H will also be present, about 1 μCi per 1 mCi of ^{18}F ingested, and lithium has therefore also been separated in this way.

Blood excretion curve and the use of ^{18}F. The presence and disappearance of fluorine in the blood, following its ingestion, has been studied by taking blood samples within 6 hours of its oral administration (Fig. 3). The disappearance attributable to radioactive disintegration has been corrected at each point so that the curve indicates only the fluorine flow to and from the blood stream. After 6 hours, no more than 10 % of the maximum amount of fluorine (at 1 hour) remained in the blood. However, it cannot be expected to be excreted to this extent (BLAU et coll. 1962, Dworkin et coll. 1965, NUSYNOWITZ et coll. 1965) which means that the fluorine must be concentrated elsewhere in the body. It is known (VAN DYKE et coll. 1965, NUSYNOWITZ et coll.) that fluorine con-

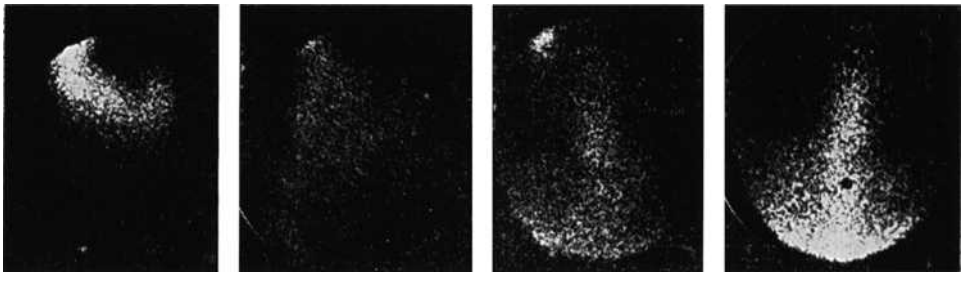

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Fig. 4. Scintillation camera views from abdominal and pelvic areas, demonstrating the flow of ^{18}F from stomach to spine. a) At 5 min after the oral dose, all the activity is still in the ventricle. b) At 20 min, the fluorine lies mainly in the intestine although the spine is already visible to the left. c) At 50 min, fluorine is seen in the middle of the lumbosacral area. d) At 3 hours, this is seen more clearly than in (c). The dots in (d) indicate the navel and processus ensiformis.

centrates in bone (Fig. 4). Fluorine has been used for two years for bone scanning in cases of primary or metastatic bone lesions and a report on these studies will be published.

SUMMARY

A method of producing ^{18}F for scanning primary and metastatic bone lesions is described. The ^{18}F may be prepared in the normal isotope laboratory of a clinic if the neutron irradiation can be effected at a laboratory within a distance of 20 km. Impurities and their influence upon the radiation dose are discussed. The behaviour of fluorine after its oral administration is considered.

ZUSAMMENFASSUNG

Eine Methode zur Herstellung von ^{18}F für Scanning bei primären und metastatischen Knochentumoren wird angegeben. ^{18}F kann in einem gewöhnlichen klinischen Istotopenlaboratorium hergestellt werden falls die Neutronenbestrahlung bei einem Ort stattfinden kann der nicht mehr als 20 km vom Istotopenlaboratorium entfernt ist. Beimischungen und deren Einfluss auf die Strahlendosen werden besprochen. Was mit dem Fluor nach der oralen Verabreichung geschieht wird ebenso besprochen.

RÉSUMÉ

L'auteur décrit une méthode de production de ^{18}F pour le diagnostic isotopique des lésions osseuses primitives et métastatiques. Le ^{18}F peut être préparé dans le laboratoire des isotopes normal d'un hôpital si l'irradiation par les neutrons peut être faite à une distance inférieure à 20 km. L'auteur étudie les impuretés et leur influence sur la dose d'irradiation. Il examine le devenir du fluor après son administration orale.

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