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A Simple Method of Producing ^{18}F Fluoride for the Study of Bone Disease[1]

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Because of the affinity of fluoride ion for bone—especially diseased bone—a suitable radioisotope of fluorine may prove a useful tool for the study of metabolic bone disease, localized osseous lesions, and dental conditions, in addition to the study of fluoride metabolism per se.

All radioactive isotopes of fluorine have short half-lives. While short lived isotopes are preferable in human studies from the standpoint of radiation dosage, methods of production involving extensive manipulation to render them sterile, pyrogen free and carrier free are rather impractical because of the time factor. The only radioactive isotope of fluorine useful for the investigative purposes outlined is ^{18}F, with a half-life of 112 minutes (1). Since it is a positron emitter, the resultant annihilation radiation is suitable for detection by the usual gamma detecting instruments, while the short half-life permits the employment of relatively high quantities with safety.

We describe herein a rapid simple method for the production of sterile, pyrogen free, carrier free ^{18}F fluoride, almost immediately available for intravenous administration without extensive manipulation, and discuss its possible applications to the study of osseous disease in man.

METHOD

Quartz ampules containing approximately 2 ml water enriched with 11.2% ^{18}O were sealed, autoclaved, and stored until used. As needed, they were processed in the Walter Reed Army Institute of Research 50 Kilowatt Thermal Water Boiler Reactor. ^{18}F, as the fluoride, is produced by the reaction:

$$^{18}O\ (p, n)\ ^{18}F$$

the proton source being generated in the water during the thermalization of fast fission neutrons. Irradiation times of approximately 150 minutes, allowing

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production of approximately 60 per cent of the theoretical maximum, were found to be convenient. After removal from the reactor and a 20 minute cooling period, the ampules were opened and the contents removed with a sterile syringe and needle.

A weighed aliquot was analyzed for its gamma emission spectrum against a ^{22}Na standard in a dual thallium activated sodium iodide crystal well counter by an RIDL 400 channel pulse height analyzer. The sample was then periodically counted in a well counter-scaler for half-life determination. Specimens were submitted for sterility and pyrogenicity checks.

RESULTS

Spectral Analysis

The results of spectral analysis are illustrated in Fig. 1. Three major peaks are noted, at 0.51, 1.02 and, relatively smaller, at 1.37 MeV. The first two are attributable to the annihilation radiation and sum peak of ^{18}F; the third peak is caused by a small amount of ^{24}Na impurity, formed by the reaction:

$$^{23}Na\ (n, \gamma)\ ^{24}Na$$

Similar results were obtained on multiple replicates.

Half-Life Determination

The count rate data is shown as a function of time in Table I and Fig. 2. The last six points obtained represent count rates at times beyond ten half-lives of ^{18}F (Table IA). The least squares regression equation for the natural logarithm of the count rate (y_1) *versus* time (x_1) was determined. The negative of the slope coefficient (b_1) is the decay constant for the longer lived radionuclide present. The physical half-life calculated from the decay constant is 920 minutes, a value within 2.2 per cent of the accepted $T_{\frac{1}{2}}$ of ^{24}Na (900 minutes) (1).

The earlier count rates of the sample were corrected for the contribution of the ^{24}Na impurity in the following manner. The average values of the last six points were used to calculate a new regression equation, the slope coefficient of which was derived from the accepted $T_{\frac{1}{2}}$ of ^{24}Na, 900 minutes. From this new regression equation, count rates attributable to ^{24}Na were computed for the earlier counting times and subtracted from the count rates obtained at those times. A plot of the logarithm of the residual count rates (y_s) as a function of time (x_s) fell on a straight line, indicating that only one other radionuclide was present (Table IB). After determining the slope coefficient (b_s) of this line, the half-life of the short-lived radionuclide was calculated to be 106 minutes, almost within the range of accepted values for ^{18}F (1).

Sterility and Pyrogenicity

Specimens were submitted to the National Institutes of Health for pyrogenicity determination. They were found to be pyrogen free. Autoclaving and irradiation rendered the product sterile.

TABLE I

DETERMINATION OF HALF-LIVES OF THE RADIONUCLIDES IN IRRADIATED ^{18}O ENRICHED WATER

A. Longer-Lived Radionuclide

Time	*Minutes From 1200 Hour, 4 Mar 64*	*Net Count Rate (cpm)*	*Ln Net Count Rate*
08:18 5 Mar	1218	1940	7.57045
09:48	1308	1849	7.52241
10:56	1376	1724	7.44240
16:50	1730	1361	7.21597
16:59	1739	1355	7.21155
19:27	1827	1184	7.07665

$\Sigma x_1 = 9198$ $\Sigma y_1 = 44.03943$

$\bar{x}_1 = 1533$ $\bar{y}_1 = 7.33990$

$b_1 = -\lambda_1 = -.00075375$

$T_{\frac{1}{2}} = \frac{.69315}{\lambda_1} = 920$ minutes

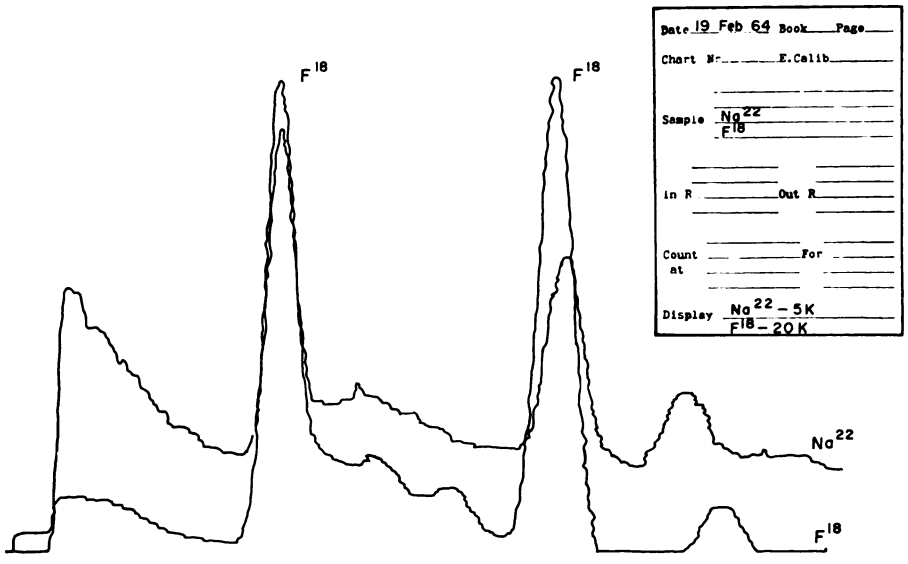

Fig. 1. Gamma emission spectra of ^{22}Na standard and irradiated ^{10}O enriched water, superimposed.

Yield

Irradiation under the conditions described resulted in a specific activity of approximately 0.9 μc ^{18}F per gram of water.

Application

To illustrate an application of the product, the rate of its disappearance from blood and the urinary excretion were studied in three adult female beagles. Blood and urine samples were recounted after decay of ^{18}F to determine counts attributable to the ^{24}Na impurity and appropriate corrections made. The data were corrected for physical decay of ^{18}F to the injection time. The results presented in Fig. 3 and Table II reflect biological events only.

Fluoride disappears from the blood in an exponential fashion with a half-time of 57 minutes (Fig. 3). Table II shows the urinary excretion data. By four hours after injection, practically all the fluoride destined to be excreted

B. Shorter-Lived Radionuclide

Time	*Minutes From 1200 4 Mar 64*	*Net Count Rate (Both Nuclides)*	*Calculated ^{24}Na Count Rate*	*Net Count Rate Short-Lived Nuclide*	*Log_{10} Net Count Rate Short-Lived Nuclide*
12:44.5 4 Mar	44.5	20,309	4849	15460	4.18921
12:46.5	46.5	20,181	4845	15336	4.18571
12:58.5	58.5	18,908	4797	14111	4.14956
13:26.5	86.5	16,250	4694	11556	4.06283
13:54.5	114.5	14,169	4595	9575	3.98114
14:14.5	134.5	13,019	4524	8495	3.92916
14:35.5	155.5	11,830	4451	7379	3.86800
15:01.5	181.5	10,507	4375	6132	3.78760
15:38.5	218.5	9,115	4252	4863	3.68690
16:09.5	249.5	8,084	4152	3932	3.59461
16:12.5	252.5	8,173	4145	4028	3.60509
16:32.5	272.5	7,447	4082	3365	3.52699
17:18.5	318.5	6,531	3940	2591	3.41347
18:53.5	413.5	5,049	3662	1387	3.14208

$\Sigma x_s = 2547$ $\quad \Sigma y_s = 53.12235$

$\bar{x}_s = 181.93$ $\quad \bar{y}_s = 3.794453$

$b_s = -.00284069$

$\lambda_s = -(2.30259)^* b_s = .0065409$

$T_{\frac{1}{2}} = \dfrac{.69315}{\lambda_s} = 106$ minutes

*To convert Log_{10} to Ln.

into the urine has been excreted, correlating well with blood levels, which are nil at four hours. The remainder of the fluoride presumably is taken up by bone.

DISCUSSION

The characteristic gamma emission spectrum and half-life establish the identity of the isotope as ^{18}F; its specific activity when produced under the conditions described is 0.9 μc per gram of water. A smaller amount of ^{24}Na impurity was also found to be present. Although the amount of ^{24}Na produced was small, it soon contributed an increasingly significant proportion of counts to the total sample. This proportion is determinable and correction can be made to obtain the activity of ^{18}F alone.

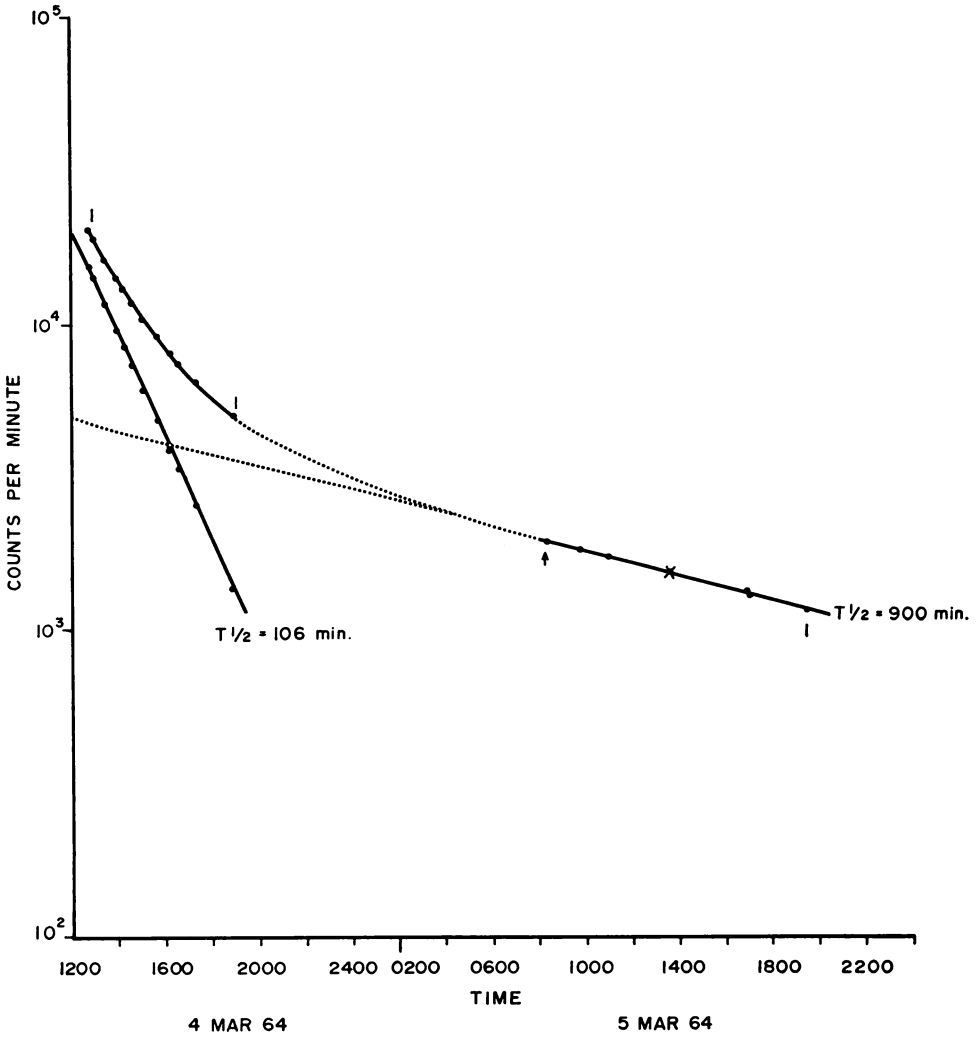

Fig. 2. Decay curve of irradiated ^{18}O eniched water. See text for explanation.

It should be noted that no specific attempt was made to remove sodium from the sample prior to irradiation, and we feel that a significant reduction of this impurity is possible. For example, the enriched water was stored in glass containing sodium; vaporization into the quartz ampules would have reduced appreciably the quantity of sodium present.

Although the specific activity of ^{18}F is low, there are several ways of increasing it significantly. First, the use of 100 per cent ^{18}O enriched water would produce a ninefold increase; second, reactors with a higher fast neutron flux would also produce a manifold increase; last, longer irradiation times, although

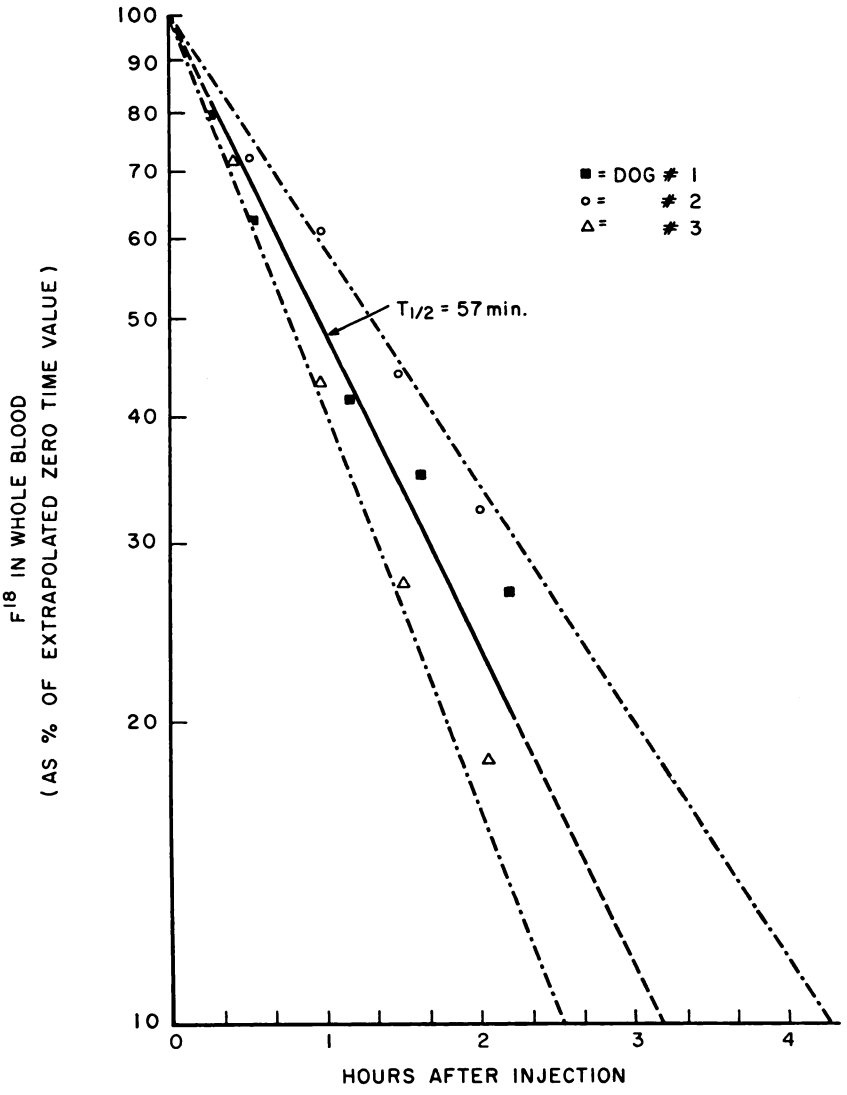

Fig. 3. Regression line for blood concentration of ^{18}F fluoride in dogs. The broken lines represent the 95 per cent confidence limits of the regression line.

least effective, would also contribute significantly. The thermal water boiler reactor used has a relatively low fast neutron flux compared to other types of reactors.

The method has two other minor advantages. Since ^{18}O is a stable nuclide, it may be stored indefinitely; further, any unused portion of water may be re-irradiated to produce ^{18}F.

The affinity of fluoride ion for bone is due to its ability to displace hydroxyl and bicarbonate ion at the surface of the apatite crystal by heteroionic exchange (2). Furthermore, fluoride uptake by normal bone is low (on the order of 10%) compared to its uptake at sites of bone lysis or formation (3), presumably because of the greater vascularity and greater exposure of bone crystal surface to the extracellular fluids of these sites. Thus, the chief factor determining the deposition of fluoride in bone is the mineral salt, and there are no large differences between bones in the availability of mineral salts for fluoride incorporation (4). Although the incorporation of fluoride into bone is not an irreversible process, its rate of release is so slow compared to the physical half-life of ^{18}F that this binding may be considered unidirectional.

Wallace-Durbin (5) found that the fluoride concentration in all soft tissues (except kidney) is in equilibrium with the blood and parallels its concentration within one hour after intravenous administration, vascular organs achieving this state much more rapidly. She also found that the ratio of fluoride concentration in bone to that in other tissues was of the order of 40 to 1 at 15 minutes.

Since blood levels of fluoride reflect levels of all soft tissues, the kidney, in the excretory process, is the only other organ competing with bone for this ion. The dogs studied excreted about 44 per cent in four hours. Approximately the same results were found in rats (5) and in man (6). Severe renal disease apparently does not significantly affect the urinary excretion of fluoride (6). Therefore, it seems likely that the distribution of tracer concentrations of ^{18}F fluoride between skeleton and kidney might be a measure of the metabolic activity of bone, as suggested by Anbar (7). Indeed, bone fluoride uptake decreases when bone resorption is inhibited by estrogens (7).

TABLE II

URINARY FLUORIDE CONTENT (% INJECTED DOSE)

Collection Period (hours)	*Dog 1*	*Dog 2*	*Dog 3*	*Average*	*Cumulative Average*
0–1	23.95	14.73	32.10	23.59	23.59
1–2	14.09	11.87	14.89	13.62	37.21
2–3	5.20	4.38	4.38	4.65	41.86
3–4	2.75	3.27	0.21	2.08	43.94
Total	45.99	34.25	51.58	43.94	43.94

Dosimetry estimates based on the retention of approximately 50 per cent of an administered dose yield values of 0.03 rads/mC administered dose for total body and 0.12 rads/mC for bone.

Blau, Nagler and Bender (3), taking advantage of the selective localization of ^{18}F to sites of bone lysis, described the scan of a localized lesion.

Although the quantities of ^{18}F fluoride which we produced are almost certainly too low for scanning, they appear to be adequate for the study of metabolic bone disease. Further studies along these lines are contemplated.

SUMMARY AND CONCLUSIONS

1. A simple method for the production of sterile, pyrogen free, carrier free ^{18}F fluoride is described. Under the conditions of production, specific activities of 0.9 μC per gram 11.2 per cent ^{18}O enriched water resulted.

2. A small amount of ^{24}Na was also present and methods for preventing the formation of this impurity are suggested. Its presence did not interfere with the use of the ^{18}F fluoride.

3. Intravenously administered ^{18}F fluoride is rapidly cleared from the blood. By four hours, 44 per cent of the administered dose appears in the urine; this represents almost the total urinary excretion of isotope. It is believed that nearly all the unexcreted fluoride is bound to bone.

4. The possible applications of ^{18}F fluoride in clinical medicine are discussed.

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