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Technetium in Biology and Medicine

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Although twenty-eight radionuclides of technetium have been prepared, only technetium-99m, technetium-99 and technetium-95m have so far become important.

Technetium-99, available in large amounts, is used in the study of the physical and chemical properties of the element, and offers the possibility of many industrial applications where its radioactivity does not create serious problems. With the increase in the use of nuclear power, however, more and more technetium-99 is being produced which is entering into the environment. This has resulted in increased interest in the biogeochemical behaviour of this radionuclide during recent years.

The ideal physical properties, half-life of 6 hours and monochromatic gamma emission of 140 kev, and the versatile chemistry of technetium-99m have recently made it the radiotracer of choice for the external noninvasive imaging of almost all internal organs of the body. In the preparation of technetium-99m radiopharmaceuticals and in the interpretation of their biological behaviour, the chemistry of technetium-99 has so far served as a guide. Similarly assumptions have been made that technetium-95m and technetium-99 have identical biogeochemical behaviour. We have shown that even the radioisomers, technetium-99m and technetium-99, have different chemical properties. These results suggest that in the study of the biological and environmental behaviour of technetium, a rigorous knowledge of the chemistry of each radionuclide is needed.

Introduction

After many unconfirmed claims [1] of the discovery of the element no. 43, the ekamanganese of Mendeleev was discovered in 1937 by C. Perrier and E. Segrè [2] in the Department of Physics of the Royal University of Palermo, Italy. As it was the first artificially made element, its discoverers gave it the name 'technetium' (symbol Tc) from the Greek word 'tekhnetos' which means artificial [3]. All isotopes of technetium are radioactive. Since the half-life of the longest-lived radionuclide, technetium-98, is only 4.2×10^6 years, which is short compared to the age of the solar system, no primordial technetium can exist on the earth. Within the period of 46 years after its discovery, 21 radioisotopes and 7 radioisomers, totalling 28 radionuclides of technetium have been prepared (Table I).

TABLE I. Radionuclides of Technetium.

Tc-90; Tc-91; Tc-92; Tc-93m, Tc-93 ; Tc-94m, Tc-94 ; Tc-95m, Tc-95 ; Tc-96m, Tc-96 ; Tc-97m, Tc-97 ; Tc-98; Tc-99m, Tc-99 ; Tc-100; Tc-101; Tc-102m, Tc-102 ; Tc-103; Tc-104; Tc-105; Tc-106; Tc-107; Tc-108; Tc-109; Tc-110.

Of these 28 radionuclides, the isomer pair, technetium-99m, technetium-99, and technetium-95m have so far become most important.

Technetium-99, which has long been available in large amounts [4, 5], has been the most convenient radionuclide of technetium for the study of its physical and chemical properties. In fact all chemistry reported in the literature is that of technetium-99. Its possible applications are [6]: 1) as a corrosion inhibitor, 2) as a superconductor, 3) as a pure beta radiation standard, 4) as an element of thermocouple, and 5) as a catalyst in organic synthesis.

Technetium-99 is a beta-emitting (E_{max} = 292 kev) radionuclide with a half-life of 212,000 yr. It may enter the environment as a result of nuclear weapon testing, nuclear fuel reprocessing, nuclear waste storage, and technetium-99m radiopharmaceutical use [7]. With the ever increasing use of nuclear power more and more technetium-99 will be produced. Kotegov and colleagues predicted that the world inventory of technetium-99 would exceed 10,000 kg by 1980 [8]. In 1975 Burkholder and colleagues estimated that the United States inventories of

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technetium-99 would reach 169,000 kg by the year 2000 [9]. These figures have led to an increased interest in the biogeochemical behaviour of technetium in the environment [10].

The ideal physical properties, half-life of 6 hours and monochromatic gamma emission of 140 kev, and the versatile chemistry of technetium-99m have made it the radiotracer of choice for external noninvasive imaging of many internal organs of the body [11]. From a recent survey on the imaging procedures (Table II) and the radionuclides used in radionuclidic imaging, technetium-99m has been found to be the most frequently used radionuclide [12].

TABLE II. Relative Frequency (in Percent) of Imaging Procedures Performed in U.S.A. in 1978 [12].

Brain	24.1
Liver	20.3
Bone	18.1
Lung	16.5
Thyroid	10.9
Renal	3.2
Tumour	2.6
Cardiac	2.5

TABLE III. Radionuclide Use Frequencies (in Percent) for Imaging in U.S.A. in 1978 [12].

Tc-99m	88.2
I-131	8.1
Xe-133	3.7
Ga-67	2.8
Tl-201	1.1
All others	0.7

It has been felt for a long time [13–15] that to achieve an improvement in the quality of technetium-99m radiopharmaceuticals and to obtain more information on the state of health of the patient with lower doses of technetium-99m radiopharmaceuticals, a rigorous knowledge of the chemistry of the radionuclide is necessary. So far technetium-99 chemistry has been a guide in the synthesis of technetium-99m radiopharmaceuticals and the understanding of their solution chemistry and biological behaviour. More recently doubts have been expressed about the validity of extending the chemistry of technetium-99, studied at millimolar level, to that of technetium-99m radiopharmaceuticals whose concentration never reaches nanomolar level [16, 17]. At such low concentrations only chromatographic and electrophoretic techniques have proved to be suitable for a comparative study of the solution chemistry of the two radionuclides and for investigating the fate of technetium-99m radiopharmaceuticals *in vivo*. In the present paper the solution chemistry of technetium-99m and technetium-99 are compared. The diagnostic application of some technetium-99m radiopharmaceuticals is reported. The effect of technetium-99 on the environment is also briefly discussed.

Experimental

Pertechnetate-99 was bought from the Radiochemical Centre, Amersham, England.

Pertechnetate-99m was eluted daily from commercial generators from Sorin Biomedica, Saluggia, Italy.

Quality control of both pertechnetate-99m and pertechnetate-99 was carried out chromatographically and electrophoretically as described by us previously [18].

All other reagents used were of high purity analytical grade from Merck.

In vivo distribution of technetium-99m was carried out with an Italelettronica rectilinear scanner or with a gamma camera from Siemens. The radioactivity in different organs of the animals was carried out with a well-type gamma counter after the death of the animal.

Technetium-99 was counted with a thin-window Geiger-Müller counter.

Results and Discussion

Chromatographic Behaviour of Technetium-99m and Technetium-99 in Different Oxidation States

Table IV gives the R_f value of the hepta-, penta-, and tetra-valent oxidation states of the two radioisomers, technetium-99m and technetium-99 in the chromatographic system: Whatman-3MM, physiological saline at 18 °C.

TABLE IV. R_f Values of Different Oxidation States of Technetium-99 and Technetium-99.

Oxidation State	R_f Value	
	Technetium-99m	Technetium-99
VII	0.64	0.64
V	0.02	0.02
IV	0.78	0.78

The results in Table IV show that the two isomers in the same chemical form have identical chromatographic behaviour. This property can be advantageously utilized in deciding the chemical composition of technetium-99m radiopharmaceuticals provided one knows the chemical composition of the similar compound technetium-99.

Comparative Study of the Reduction of Pertechnetate-99m and Pertechnetate-99 by Hydrochloric and Hydrobromic Acids

In order to compare the solution chemistry of the two radioisomers, technetium-99m and technetium-99, the reduction of the pertechnetate-99m and pertechnetate-99 was carried out with concentrated hydrochloric acid [19] and concentrated hydrobromic acid [20]. The results can be summarized as follows:

1) Both acids reduce pertechnetate-99 more slowly than pertechnetate-99m. At room temperature the pertechnetate-99 needs aging for more than two years to produce chromatographically pure technetium-99 (IV) with concentrated hydrochloric acid. This reduction is complete within 10 hours for pertechnetate-99m. The rate of reduction is still faster with concentrated hydrobromic acid.

2) The reduction of both pertechnetate-99m and pertechnetate-99 proceeds to the tetravalent technetium via technetium(V) as an intermediate product. The intermediate product, technetium-99(V), could be isolated pure and its chemical properties studied [21]. The reduction of technetium-99m(V) to technetium-99m(IV) being very rapid [19, 20], pure samples of technetium-99m(V) could not be isolated.

Thus there is a considerable possibility of preparing technetium-99(V) complexes [22], but the preparation of technetium-99m(V) radiopharmaceuticals in the presence of stannous chloride, the most commonly used reducing agent in Tc-99m radiopharmaceutical synthesis, is not likely because it is a stronger reductant than hydrochloric acid or hydrobromic acid.

From the above results it is concluded that the two radioisomers, technetium-99m and technetium-99, have different solution chemistry. In order to prepare pure technetium-99m readiopharmaceuticals and to study their biological behaviour a thorough study of the solution chemistry of technetium-99m is, therefore, necessary.

Biological Behaviour of Technetium-99m

Due to its widespread use in diagnostic nuclear medicine, there is a great interest in the biological behaviour of technetium-99m. Great efforts are being made to produce organ specific and disease specific technetium-99m radiopharmaceuticals. Following are some examples.

Pertechnetate-99m as a Radiopharmaceutical

Pertechnetate-99m is the most stable form of the radionuclide and is routinely used in the imaging of the thyroid gland (Fig. 1), salivary glands and brain lesions (Fig. 2).

We have shown [23] that this ion concentrates in the thyroid by anion exchange mechanism and is not metabolized.

Liver Imaging with Technetium-99m Sulphocolloids or with Technetium-99m Phytate

Figure 3 shows a typical scintigram of the liver by intravenous administration of technetium-99m sulphocolloid or phytate. If some lesion is present reduced uptake of the radionuclide in that region is observed.

Spleen Imaging with Technetium-99m-red Blood Cells

The scintigraphic image of the spleen with technetium-99m labelled red blood cells is shown in Fig. 4. Here again the pathologic state of the organ is shown by a lack of radionuclide uptake in this region.

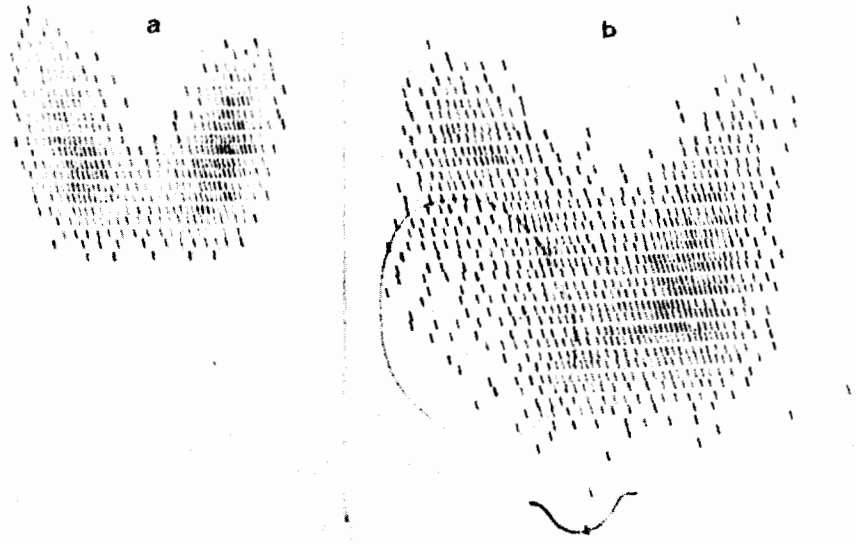

Fig. 1. (a) Normal and (b) pathologic thyroid scintigram with pure pertechnetate-99m.

Fig. 2. Brain scintigram showing lesion (arrow head) with pure pertechnetate-99m.

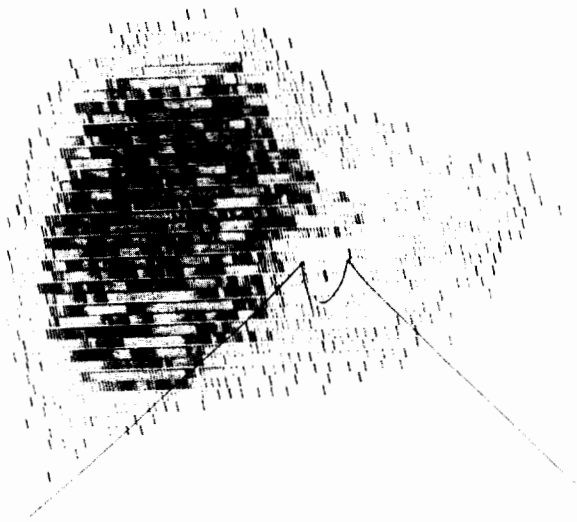

Fig. 3. Normal liver scintigram with technetium-99m phytate.

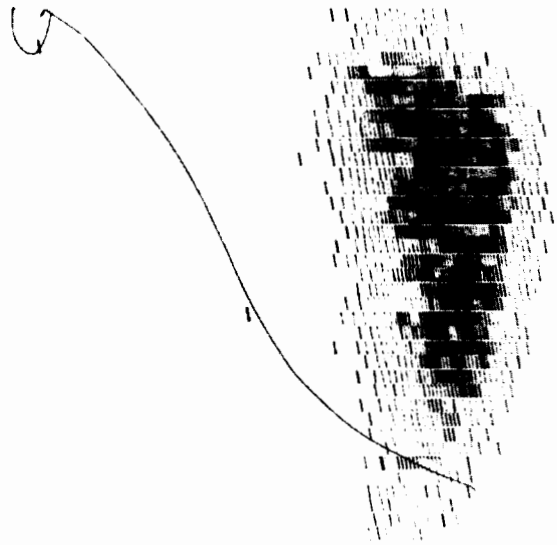

Fig. 4. Normal splenic scintigram with technetium-99m labelled red blood cells.

Renal Imaging with Technetium-99m Dimercaptosuccinate

Technetium-99m dimercaptosuccinate (Tc-99-DMSA) is today the most widely used radiopharmaceutical for the imaging of kidneys. Figure 5 shows the normal kidney scintigram of a patient. The renal pathological state is shown by the lack of radionuclide uptake.

Bone Imaging with Technetium-99m Diphosphonates

Technetium-99m methylenediphosphonate (Tc-99m-MDP) has been until recently the most common bone imaging agent. Technetium-99m hydroxymethylenediphosphonate (Tc-99m-HMDP) and technetium-99m 1,2-dicarboxypropane-3,3-diphosphonate (Tc-99m-DPDP) are recently introduced

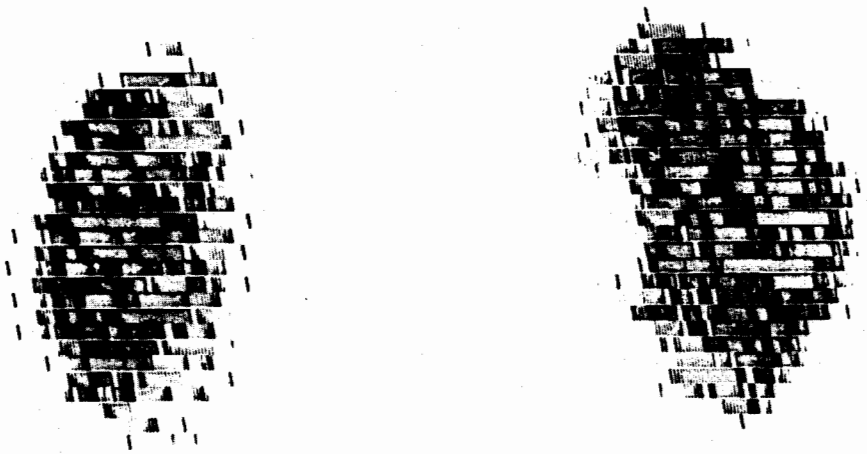

Fig. 5. Normal renal scintigram with technetium-99m-DMSA.

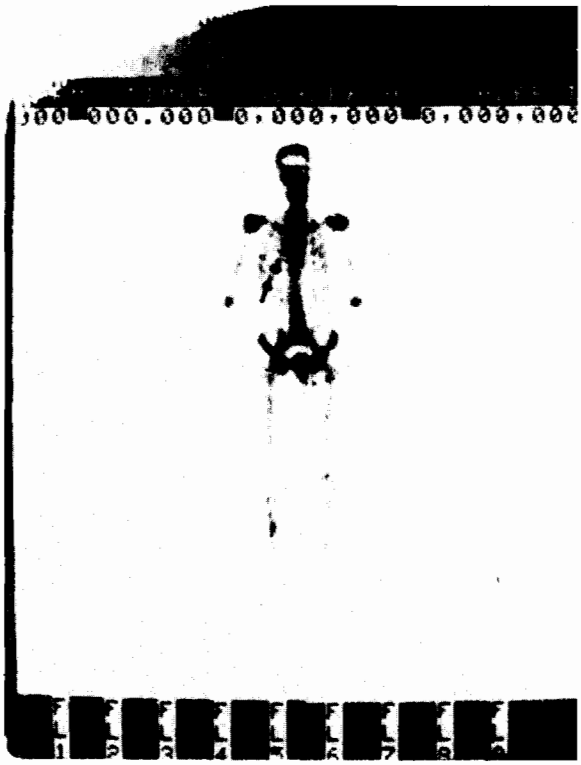

Fig. 6. Bone image with technetium-99m-HMDP showing a metastatic bone tumour (arrow head).

bone imaging agents. Tc-99m-HMDP gives high quality bone images when early scintigrams are needed. High bone-to-soft tissue activity images with Tc-99m-DPDP are obtained after about four hours after the injection of the radiopharmaceutical. Figure 6 shows the bone image of a patient with Tc-99m-HMDP where the metastatic tumour in one rib has been visualized (shown by the arrow head) as the point of intense uptake of the radionuclide.

For most technetium-99m radiopharmaceuticals, the purity of the preparation, composition and structure are still unknown [24]. In order to understand the mechanism of *in vivo* behaviour, a systematic study of the solution chemistry of each radiopharmaceutical and the *in vivo* behaviour of chromatographically pure radiopharmaceuticals is in progress in our laboratories.

Biogeochemical Behaviour of Technetium-99 in the Environment

Wildung and colleagues [7] have recently discussed the various sources of technetium-99 in the environment and what is known about its behaviour. The studies of Gearing and colleagues [25] on the biochemical effects of the pertechnetate-99 ion on microorganisms have shown that the pertechnetate-99 ion has a biochemical effect on cells, unrelated to the radioactivity or the oxidation state of the radionuclide.

Bioaccumulation of technetium-99 in marine organisms has been recently studied by Fischer [26] and by Beasley and his colleagues [27]. The results indicate that phytoplankton are likely to have negligible influence on the cycling of technetium-99 in marine systems.

In studies on the biogeochemical behaviour of technetium-99, the researchers have often used technetium-95m in the laboratory experiments. So far the studies have not been reported to show that technetium-99 and technetium-95m have identical solution chemistry. Such studies are also in progress in our laboratories.

Conclusions

Technetium-99m, having ideal physical properties of the external noninvasive imaging of internal organs

of the human body, needs an exhaustive study of its solution chemistry because it is in this form that technetium-99m radiopharmaceuticals are administered.

Technetium-95m, used as a tracer in the biogeochemical behaviour of technetium-99, also needs comparative study.

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