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4. POTENTIAL MEDICAL APPLICATIONS OF RUTHENIUM ISOTOPES

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INTRODUCTION

The preparation of radioactive isotopes (radionuclides) for use in medical diagnosis (nuclear medicine) has been reviewed in the purely chemical literature before [1] and the role of metal ions, in particular, in biological systems has been the subject of a number of articles [2–6]. However, as this topic has not been previously covered by this journal, a number of words of introduction would be appropriate.

One of the basic procedures in nuclear medicine involves the administration to a patient of a radionuclide in some suitable chemical form that can be subsequently detected externally while the compound undergoes *in vivo* metabolism. The methods used to trace these compounds rely on the fact that the radionuclide chosen for the study will emit γ-radiation. The subsequent absorption of this radiation in a suitable detector is often referred to as scintigraphy.

In the early application of the technique, γ-emitting radionuclides of some of the physiological elements were injected in simple chemical forms, such as radioiodine (^{131}I) for thyroid function measurements [7], and radiolabelled carbon dioxide ($C^{15}O_2$) for lung function measurements [8]. As nuclear medicine developed, metal-ion radionuclides were quickly introduced; not for any physiological reason, but for their excellent physical properties which optimised the scintigraphy technique [9]. These metal radionuclides (^{67}Ga; $^{99}Tc^{m}$; ^{111}In), which are now being used for routine application, are administered in the main as simple ionic compounds, but as the understanding of the *in vivo* fate of these

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materials increases, the need is becoming apparent for the development of sophisticated compounds labelled with these metals, which have a specific metabolic rôle.

4.1 RUTHENIUM RADIONUCLIDES

It was partly on the basis of its excellent physical properties that ruthenium-97, in particular, was recognised as a potential radionuclide for nuclear medicine by Subramanian, McAffee and Poggenburg in 1970 [10].

Ruthenium-97 has a half-life ($t_{\frac{1}{2}}$) of 2.84 days [11], and decays solely by electron capture to ^{97}Tc ($t_{\frac{1}{2}}$ 2.6 x 10^6 y) with the emission of two prominent γ-rays at 216 keV (86%) and 325 keV (10%) [12]. Its decay characteristics are compared with a selection of other possibly useful ruthenium isotopes in Table 1.

TABLE 1

Summary of decay data for ruthenium radionuclides

Mass Number	Half-life ($t_{\frac{1}{2}}$)	Principle Mode of Decay	Gamma-Ray Transition Energies/keV	Suitability for *in vivo* Scanning
Ru-94	51.8 m	EC [a]	367,892	Poor
Ru-95	1.65 h	EC + β^+ (15%) [b]	336,1097,627	Poor (but may have use in PECAT scanning [c])
Ru-97	2.84 d	EC	215,325	Excellent
Ru-103	39.4 d	β^-	497	Poor
Ru-105	4.44 h	β^-	724 + many others	Poor
Ru-106	368 d	β^-	no γ rays	Not considered

[a] EC Electron Capture [b] β^+ Positron emission giving 511 keV gamma radiation (Annihilation radiation) [c] PECAT Positron emission computerised axial tomography (See "Seminars in Nuclear Medicine", *9* (1980); *10* (1981))

Though ^{97}Ru is the radionuclide of choice for nuclear medicine applications, many of the preliminary studies involving ruthenium compounds have been carried out using the longer-lived ^{103}Ru or ^{106}Ru, which are available commercially [13]. These are prepared from the neutron irradiation of stable ruthenium and suffer from inevitable poor specific activity. This means that the radioactive atoms of ^{103}Ru/^{106}Ru produced are "diluted" with the non-radioactive atoms of the stable ruthenium target material. The neutron deficient isotopes on the other hand

(^{94}Ru, ^{95}Ru and ^{97}Ru) can only be produced from charged particle irradiations, which use a different element for the target material and are thus available as "carrier-free". The nuclear reactions which have been used to produce these nuclides are summarised in Table 2.

TABLE 2

Production of the neutron deficient isotopes of ruthenium

Target[a]	Nuclear Reaction	Product	Reference
Mo (natural)	^{3}He, xn	^{94}Ru	14
Mo (natural)	^{4}He, xn	^{94}Ru	14,15
Mo (natural)	^{3}He, xn	^{95}Ru	14,16
Mo (natural)	^{4}He, xn	^{95}Ru	14,15,16
^{99}Tc	p, 3n	^{97}Ru	17
^{103}Rh	p, 2p.5n	^{97}Ru	18,19
Mo (natural)	^{3}He, xn	^{97}Ru	14,16,20
Mo (natural)	^{4}He, xn	^{97}Ru	11,14,15,16,21,22
Possible contaminants in ^{97}Ru			
^{100}Mo	^{4}He, n	^{103}Ru	11,14,15
^{100}Mo	^{4}He, p	^{103}Tc → ^{103}Ru	15

[a] Mo (natural) consists of ^{92}Mo(14.8%), ^{94}Mo(9.1%), ^{96}Mo(16.7%), ^{97}Mo(9.5%), ^{98}Mo(24.4%) and ^{100}Mo(9.6%)

The ^{4}He (alpha particle) irradiation of natural molybdenum appears to have received the most attention, but unfortunately contamination by the longer lived ^{103}Ru occurs [11,14,22]. This would be completely eliminated using the ^{3}He reactions [14,16,20] and spallation route [18,19], or by the proposed use of enriched targets depleted in ^{100}Mo [22]. Elimination of the ^{103}Ru content would be desirable for most nuclear medicine applications in order to reduce the total radiation dose to the patient: radiation dose from ^{103}Ru is a factor of 2.5 greater than that from ^{97}Ru for each unit of radioactivity [23].

The methods used for the separation of radioruthenium from charged particle irradiated targets have included co-precipitation [17,21], solvent extraction [11,16,19], wet distillation of RuO_4 [18,19,21] and differential sublimation [11]. However, Pao *et al.* [22], while working in the author's laboratory, considered that none of these methods were rapid or simple enough to be used for the routine preparation of ^{97}Ru and developed an ion-exchange separation

using tin(IV) oxide. Investigations with larger scale production targets have necessitated modification of this technique, resulting in usable quantities of ^{97}Ru which are now available for labelling purposes.

4.2 RUTHENIUM COMPOUNDS WITH POTENTIAL APPLICATIONS IN NUCLEAR MEDICINE

For the maximum clarity and convenience, the remaining text is sub-divided into headings covering groups of compounds that have a more biochemical classification than the purely chemical approach usually found in these reviews. Many of the cited publications are from proceedings of international symposia which are published in a collection of short abstracts and often contain a minimum of experimental details. This is indicated in the text where appropriate.

It is also worth mentioning at this point that there are many problems associated with the general availability of ^{97}Ru because of the necessity of charged particle irradiations and its relative short half-life of 2.84 days [24,25]. Thus the majority of the nuclear medical applications cited have utilised ^{103}Ru in the initial studies.

The impetus for much of the early work with radiolabelled ruthenium compounds was as a result of the potential hazards from the human ingestion of ^{103}Ru and ^{106}Ru products in nuclear waste [26-31]. This information, though not directly applicable to nuclear medicine procedures, has provided the basis of the bio-distribution data of the compounds which follow.

4.2.1 Ruthenium(III) chloride[†]

The usefulness of radiolabelled ruthenium(III) chloride as a potential subcutaneous tumour localising agent was investigated by Tanabe and Yamamoto in 1975 [32], by Mizukawa *et al.* in 1978 [33], and some clinical trials with patients were reported by Tanabe in 1976 [34]. It has previously been shown [35] that transformed cancer cells were stained more intensely with "ruthenium red" (see Section 4.2.2) than normal cells, indicating a possible preferential uptake of ruthenium. As the mechanism of binding affinity had not been clarified, there was a possibility that ionic ruthenium itself was being metabolised. The investigations showed that certain tumours could be delineated in rats by scintigraphy and that ^{97}Ru in particular would be the isotope of choice for this purpose in patients. The clinical trial with thirty-seven patients using ^{103}Ru resulted in a similar conclusion. However, these results did not offer any

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[†] The impure nature of commercial ruthenium(III) chloride has been discussed elsewhere [78; p.87].

significant benefit over the widely used gallium citrate (labelled with ^{67}Ga; $t_{\frac{1}{2}}$ 3.26 d) which was first used for the localisation of human soft tissue tumours some years earlier [36,37].

The sub-cellular distribution and mechanism of binding of ruthenium(III) chloride in tumours was the subject of a study by Mizukawa [38], who showed that the tumour affinity for "ruthenium" was related to the specific binding of glycopeptides on the cell surface of the tumour.

4.2.2 "Ruthenium red" and other ruthenium ammine complexes[+]

The cytological dye "ruthenium red", has been shown to selectively bind to mucopolysaccharides [39,40], which are found in abundance around certain tumours [41,42]. It was these characteristic interactions that led Anghileri to suggest that radiolabelled "ruthenium red" might be used to produce a tumour-specific scanning agent [43, 44]. The distribution studies in tumour bearing animals [44] confirmed the above hypothesis, showing an accumulation in tissues known to contain an appreciable amount of mucopolysaccharides and mucoproteins (*e.g.* bone, stomach and ovary). These findings were later endorsed in a published abstract by Petitjean *et al.* [20], but the animal tumour model chosen for this study showed no specific affinity for the labelled compound.

Erythrocytes (red blood cells), which have a cell membrane rich in mucopolysaccharides, have also been "tagged" using ^{103}Ru labelled "ruthenium-red" [45], but with a poor labelling efficiency. Interest in this compound diminished as more efficient radiolabelling agents for cellular blood elements became available for routine clinical use [46, 47].

It should be noted that the chemical characterisation of the radiolabelled "ruthenium-red" used for these studies does not appear to have been carried out, thus reflecting the preliminary nature of the results. However, some ruthenium(III) ammine complexes which have attracted recent attention have, on the other hand, been subjected to more rigorous chemical identification procedures.

Thus chloropentaammineruthenium(III) dichloride, $[Ru(NH_3)_5Cl]Cl_2$, incorporating ^{103}Ru, has been synthesised, and its purity checked [48–50]. The ability of the compound to act as a tumour localising agent was tested in an animal model, but it showed no distinct advantage over ruthenium(III) chloride [48]. Complexation of the ruthenium ammine compound with a number of amino

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[+] The structure of a salt derived from "ruthenium red", $[Ru_3O_2(NH_3)_{14}][S_2O_3]_3.4H_2O$ has recently been determined [78; p.86].

acids, L, (to give $[Ru(NH_3)_5L]Cl$) was attempted in the hope of developing a ruthenium pancreatic imaging agent. This was reported in an abstract by Meyer and Davis [49]. The 4-pyridylalanine complex, labelled with ^{103}Ru, showed particularly good characteristics for such an agent, having a maximum pancreas-to-liver ratio of 17.0. This is considerably higher than reported values of about 2.5 measured for the commonly used compound for these studies, ^{75}Se labelled selenomethionine [51].

The preparation of aquapentaammineruthenium(II) dichloride, $[Ru(NH_3)_5(H_2O)]Cl_2$, has also been briefly mentioned in the abstract by Subramanyam *et al.* [50], and its reaction with an antibody (IgG) has resulted in the formation of a stable complex. The authors propose to extend their studies of the labelling procedure to other proteins.

4.2.3 Other ruthenium complexes

Diethylenetriaminepenta acetic acid ($dtpaH_5$) labelled with ^{111}In ($t_{\frac{1}{2}}$ 2.83 d) has been shown to be of value for studying cerebrospinal fluid (CSF) in the technique known as cistenography [52]. However, Oster and co-workers [24] remarked that ^{97}Ru may offer some advantages over ^{111}In as a label for the chelate in terms of a reduced radiation dose to the patient and better imaging quality with a gamma camera. Their experiments using ^{103}Ru and ^{97}Ru DTPA in mice and dogs showed that the kinetics and excretion of the ruthenium chelate were unaltered from the ^{111}In labelled compound. The authors also concluded that on a purely nominal radioactivity scale ^{97}Ru delivers approximately half the absorbed dose to tissues compared with ^{111}In. However, this may not be the case at the cellular level where the radiation doses appear to be more comparable [53].

Another chelate studied by this group was 2,3-dimercaptopropane sulphonic acid (dmsa). Their experiments with ^{97}Ru dmsa in dogs has been described in abstract form [54,55] and it appears that the complex may be useful for delayed renal imaging. In a paper by Anghileri *et al.* [56], a similar conclusion was reached after experiments with ^{103}Ru labelled dmsa involving rats and rabbits. A probable mechanism to explain the renal accumulation is suggested by the authors, which involves the bonding of the ruthenium-dmsa complex to metallothionein. This protein has been shown previously to avidly bind Group IIB metals [57].

A proposal has also been made to use ^{97}Ru as a replacement for the short-lived $^{99}Tc^m$ ($t_{\frac{1}{2}}$ 6 h) in the complex *N*,α-(4-isopropyl-acetanilide)iminoacetic acid (pipida) to extend the period of its use for studying the biliary tract [25]. Studies involving dogs and rats showed a similar tissue distribution and

rate of excretion for both the $^{99}Tc^{m}$ and ruthenium labelled complex.

Various 8-hydroxyquinoline (oxine) derivatives labelled with radio-ruthenium have been prepared, and the ruthenium-oxine-7-carboxylic acid complex, in particular, has shown some promise as a tumour localisation agent in the experimental animal model described by Srivastava *et al.* [48]. However, a more useful application for the ruthenium oxine type complexes may turn out to be in the field of human blood cell labelling. At present ^{111}In-oxinate (and ^{111}In-acetylacetonate) are being widely used clinically for labelling cells [58,59], which are subsequently used for the diagnosis of abnormal lesions (abscesses, inflammatory processes, thrombosis, *etc.*). In order to achieve a high labelling efficiency of the cells, they must be washed free of plasma before labelling as, in the presence of plasma proteins, indium avidly binds to transferrin [60]. It was pointed out in an abstract by Zoghbi *et al.* [61] that ionic ruthenium is not expected to bind to blood proteins so rapidly. This would enable cell labelling using ruthenium complexes to proceed in the presence of plasma and thus avoid the cell damage associated with plasma removal. Of the various complexes studied in this way, ruthenium oxinate appeared to give the best labelling efficiency for platelets (*ca.* 55%) [47,61]. On the other hand, the ruthenium tropolonate complex, which was also evaluated by this group, gave an unexpectedly poor incorporation, especially when consideration is given to the recently reported clinical success of the indium tropolonate complex [62]. It is clear from these studies (and those in our laboratories) that many variables affect these labelling procedures, and the search for the optimum conditions is continuing.

Another reason put forward by Zoghbi *et al.* [61] for the potential use of ruthenium complexes in cell labelling was the expected reduction in the radiation dose at the cellular level (compared to ^{111}In) which should increase viability *in vivo*. It appears, however, that these radiation dose calculations are in doubt [53], but it is unlikely that this will deter the further study of ruthenium complexes which are turning out to be a useful complement to the successful indium compounds.

It is interesting to report that, though ionic ruthenium has been prepared for cell labelling in plasma because it is not expected to bind very rapidly to transferrin, the ruthenium transferrin complex has in fact been prepared and tested as a possible tumour localising agent in an animal model [48]. The preparation involved reacting ruthenium activity with "iron free" human transferrin at pH7 for 2 h at 40 °C. Purification of the monoruthenium transferrin was accomplished using a G-150 Sephadex column. Injection of this compound into tumour bearing mice resulted in a superior tumour uptake compared to all other ruthenium compounds previously discussed (*viz* ruthenium oxine-

7-carboxylic acid, ruthenium oxinate, chloropentaammineruthenium(III) dichloride and ruthenium(III) chloride). This result would appear to support the hypothesis of the presence of transferrin receptor sites on the surface of tumour cells, though as Hoffer has pointed out in the case of gallium transferrin [37], the mechanism of uptake by the tumour is likely to be more complicated than this explanation suggests.

This apart, ruthenium transferrin (labelled with ^{97}Ru) would compare extremely well with other agents (*e.g.* gallium-67 citrate) in use at present for tumour localisation, because of its selectivity, reduced whole body radiation dose to the patient, and its excellent physical properties for scanning purposes.

4.2.4 Organoruthenium complexes

A number of investigations into the preparation and uses of labelled ruthenocene derivatives have been made by Wenzel and his co-workers [63-73], beginning with the synthesis of radioactive metallocenes using ferrocene as a precursor [63]. Subsequent separation of the compounds, labelled with ^{59}Fe, ^{103}Ru and ^{181}Os, was made using thin layer chromatography.

The metabolic fate of the ruthenocene parent compound was studied by Taylor and Wenzel [64], using an animal model. They showed that ruthenocene had a much higher *in vivo* stability than ferrocene, being eventually eliminated from the body through the bile and urine following hydroxylation and formation of a glucoronide conjugate in the liver. It was hoped that by derivativising the cyclopentadienyl rings of ruthenocene, radioactive ruthenium may be encouraged to localise in specific tissues, so producing imaging agents for diagnostic purposes.

Thus the ^{103}Ru ruthenocene carboxylic acid derivative was prepared and its metabolism investigated in mice [65]. The results indicated that as the compound was rapidly excreted *via* the kidneys, it may show promise as a renal imaging agent. The oestrogen esters of ruthenocene carboxylic acid have also been studied as possible localising agents for adrenals, ovary and uterus, but unfortunately they exhibit their highest concentration in the kidneys and liver [66]. Other derivatives have shown a more appreciable uptake in the adrenals, for example the acetylruthenocene derivatives [67,68], but their localisation in other close organs may preculde their use as an agent for adrenal imaging. The cinnamoyl and 3-phenylpropen-1-one derivatives of ruthenocene labelled with ^{103}Ru have been studied and found to be avidly taken up by thymus tissue after intraperitoneal administration to mice and rats [69]. The *N*-methyl-*N*-β-chloroethylhydrazone derivatives of ferrocene and ruthenocene

aldehydes have also been synthesised [70]. The metabolism and organ distribution of the ruthenium derivative showed a high affinity for lung tissue, and appeared to exhibit cytostatic effects similar to that of benzaldehyde hydrazone. Possible clinical applications for those compounds may result from these studies.

Some ruthenocene derivatives have been examined for tumour localising properties. Of these the vinyl benzoyl- and di(methylcarboxylate) derivatives have exhibited favourable tumour-organ ratios relative to the widely used ^{67}Ga-citrate [71].

More recently, amino-sugar derivatives of ruthenocene (glucosamine, galactosamine and mannosamine) have been synthesised [72], and their metabolic fate studied in mice [73]. These experiments have shown that the kidney and liver concentrations of the compounds are high, and that the injected amino-sugar derivative is excreted in the urine unmetabolised, once again demonstrating the *in vivo* stability of the ruthenocene compounds.

4.2.5 Antineoplastic agents

The "anti-cancer" drug bleomycin (BLM) has been labelled with ^{103}Ru, in a synthesis taking about an hour, with yields of the product containing up to 50% incorporation of the radioactivity with "carrier free" ^{103}Ru [74]. The compound prepared in this way using ^{97}Ru would be the first radioactive label for bleomycin to meet the various criteria required to make it the ideal tracer for *in vivo* applications. That is, the labelling process and separation are simple to manage on a routine basis giving a quantity of pure product suitable for *in vivo* uptake studies. In addition, the compound is stable enough to store before use and, more importantly, exhibits the same *in vivo* distribution and metabolic properties as those of the unlabelled bleomycin. This being the case, the ^{97}Ru labelled product, when available, should find many applications in studying the distribution and action of bleomycin on human tumours.

Another possibility that has been suggested by the authors is that if the ruthenium bleomycin were labelled with the high energy beta emitting isotope of ruthenium, ^{106}Ru ($t_{\frac{1}{2}}$ 368 d), it could be used as an *in vivo* radiotherapeutic agent, delivering a radiation dose specifically to the tumour. The use of ^{106}Ru "applicators" in this respect has already been reported for the treatment of eye tumours (malignant melanomas of the choroid) by Lommatzsch [75,76].

Finally, it should be noted that many ruthenium compounds are being investigated for their antitumour properties in the hope of finding a therapeutic agent to compare with the *cis*-platinum(II) drugs (*e.g. cis*-$[PtCl_2(NH_3)_2]$) [77]. If, and when, such agents are found suitable for treating

tumours *in vivo*, radiolabelling with ^{97}Ru would result in an interesting class of compounds for scintigraphic studies.

4.3 CONCLUSIONS

Labelled compounds containing ruthenium appear to have a number of potential applications in nuclear medicine. Amongst the most important is the possible replacement of ruthenium for technetium in a wide range of diagnostic agents that at present contain the short-lived $^{99}Tc^{m}$. The resulting extension of the period over which many of these agents could be studied would greatly assist the clinical assessment of these compounds. The replacement by ruthenium in complexes which have been labelled with indium radionuclides also appears to have certain advantages, but comparison of the radiation dose needs careful study.

With the possibility of antineoplastic agents containing ruthenium being used clinically, a radioactive tag suitable for *in vivo* scanning would be a distinct advantage. Although much, if not all, of these initial investigations involved the use of the isotope ^{103}Ru, the shorter lived ^{97}Ru would be an almost ideal label from a scintigraphy point of view. At the moment supply of this radionuclide is limited to specialised institutions, due to the necessary inconvenience of charged particle irradiation using accelerators. However production *via* the spallation route does hold out the possibility of commercial availability, in the USA at least.

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