THE YEAR BOOK of NUCLEAR MEDICINE

VOLUME 4—1969

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EDITED BY

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INTRODUCTION

In 1968, the Third International Radioisotope Scanning Conference was held in Salzburg under the sponsorship of the International Atomic Energy Agency. These proceedings were published in early 1969 under the title *Medical Radioisotope Scintigraphy,* which I imagine will be the final term used to describe both rectilinear scanning and static camera imaging. Several papers presented at that meeting are included in this volume, which I hope makes this book as current as books can be.

In the United States, the move for certification of physicians in Nuclear Medicine is progressing with the support of the Boards of Medicine, Pathology and Radiology. Currently, there are approximately 100 physician slots available for postinternship or residency training in Nuclear Medicine for periods of 1-2 years. This no doubt will expand when a proper avenue of certification is finalized.

Indium-113m appears to be on the way out as technetium-99m radiopharmaceutical production in hospitals becomes less complicated by the use of kits for liver scanning agents and the easier aggregation of tagged compounds for lung scanning. Also, the 140-kev energy of ^{99m}Tc is better than ^{113m}In for dynamic camera studies.

The editor is grateful for the continuing trickle of criticisms on how to improve these volumes. Dr. Michael Welch of Washington University graciously consented to write this year's lead article on the very important field of radiochemistry.

JAMES L. QUINN, III

THE ROLE OF THE CHEMIST IN NUCLEAR MEDICINE

by MICHAEL J. WELCH, PH.D.*

By glancing through this YEAR BOOK OF NUCLEAR MEDICINE and the preceding editions, one can see the many scientific disciplines covered by the articles discussed. Nuclear medicine encompasses the fields of the physician, the physicist, the chemist and the biochemist. For nuclear medicine to progress as a true science it is essential that it becomes an interdisciplinary science. The scope of this article is to discuss the author's opinions as to the role of the chemist in the interdisciplinary framework of nuclear medicine.

The role of the chemist can be divided into two parts: firstly, the understanding of radiopharmaceutical preparations already in use, initially prepared to a great extent by trial and error, and secondly, the preparation of new radiopharmaceuticals. This latter category could be further divided into three sections: (1) preparations involving isotopes currently in use, (2) preparations using very short-lived accelerator-produced isotopes and (3) preparations involving the substitution of a radioisotope for a different element of very similar chemical properties. Radiopharmaceuticals produced by the last two methods are labeled metabolites.

In this article, the examples cited will be taken mainly from work currently under investigation at our institute, and the examples are intended to show the various types of chemical research being performed in nuclear medicine. A more comprehensive set of examples is, of course, given in the chapter of the YEAR BOOK covering radiochemistry and radiopharmacology.

Indium Chemistry

A good example of chemistry aiding the understanding of a radiopharmaceutical preparation is in the understanding of the indium generator and its subsequent organ-specific preparations.[1] The eluate of a tin-113, indium-113 generator, either alone or with the addition of sodium chloride and slight pH adjustment, has been advocated for blood pool scanning.[2,3]

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The eluate should contain various indium chloride species ($In(H_2O)_6^{+++}$, $In(H_2O)_5Cl^{++}$, $In(H_2O)_4Cl_2^{+}$, $In(H_2O)_3Cl_3$, etc.), but the literature values of the equilibrium constants of these species vary so much that it is impossible to assess the eluate chemical composition. By considering different literature values[4] for the equilibrium constants, one can calculate eluate compositions as diverse as % $In(H_2O)_6^{+++} = 4.4$ or 24.2; % $In(H_2O)_5Cl^{++} = 72.1$ or 31.5; or % $In(H_2O)_4Cl_2^{++} = 23.5$ or 44.2. In these calculations, species containing more than two chlorine atoms are neglected. It is possible to separate $In(H_2O)_6^{+++}$ from the chloride-containing indium species on an ion exchange column, and so calculate the equilibrium constant of the reaction

$$In(H_2O)_6^{+++} + Cl^- \rightleftharpoons In(H_2O)_5Cl^{++} + H_2O.$$

From data obtained by absorbing various chloride-containing indium species on batches of ion exchange resin and observing the fraction absorbed, it is also possible to evaluate the equilibrium constants. One can compare the values from the separation method with the batch absorption method, and the values obtained by the two methods agree to better than 1%, so it appears that the eluate of an indium generator eluted with 0.05N hydrochloric acid is $In(H_2O)_6^{+++} = 5.85\%$, $In(H_2O)_5Cl^{++} = 80.50\%$, $In(H_2O)_4Cl_2^{+} = 11.65\%$, $In(H_2O)_3Cl_3 = 2.00\%$, whereas the composition of the indium chlorides at isotonic chloride concentration is approximately $In(H_2O)_6^{+++} = 2.55\%$, $In(H_2O)_5Cl^{++} = 70.00\%$, $In(H_2O)_4Cl_2^{+} = 20.40\%$, $In(H_2O)_3Cl_3 = 7.00\%$. It appears that chemically the generator eluate and a blood pool preparation at isotonic chloride concentration are very similar, and so can be expected to have similar physiologic behavior. To alter the chemical composition significantly, the chloride concentration would have to be altered by much more than the small factor involved in obtaining an isotonic solution.

Another area of clinical nuclear medicine where the known chemistry of indium is of assistance is in the preparation of chelates for brain scanning agents. In aqueous solution above pH 2.7, insoluble indium hydroxide is formed, and preparation of the indium chelates (with DTPA or EDTA) with a final pH of 7 involves more than one manipulation. Indium can, however, be kept in solution of pH 7 by simply adding acetate or tartrate[5,6] in very low concentration. By eluting the generator into a mixture of acetate, the chelating agent and sufficient

buffer to bring the final pH to 7, a very effective indium chelate can be formed by a single step process if the chelating agent is in excess of the acetate.[7]

Short-Lived Isotopes

Having briefly given examples for the use of chemistry in the understanding of current radiopharmaceutical preparations and the simplification of preparations, we will now proceed to the subject of the preparation of metabolic traces labeled with short-lived accelerator-produced isotopes.

The potential of the short-lived isotopes of oxygen (2-minute half-life oxygen-15), nitrogen (10-minute half-life nitrogen-13) and carbon (20-minute half-life carbon-11) has been discussed in some detail.[8,9] The major problem in the utilization of these isotopes is the ingenuity required to label useful biomedical compounds with these isotopes. Because such preparations are major research projects in themselves, before they are attempted there should be much discussion among all the disciplines involved in nuclear medicine as to the potential worth of the compounds and to the amount of activity necessary. Although the small cyclotron is the most popular accelerator in use in nuclear medicine, it is worthwhile discussing, in general, the methods of production of the short-lived isotopes. The example that will be used is carbon-11; the various methods of production are equally applicable to nitrogen-13 and oxygen-15. Table 1 shows the various methods of producing carbon-11 and includes conservative estimates of the amount of carbon-11 that can be produced. It is seen from this table that several of the methods involved production of carbon-11 from carbon-12, and at first sight this would point to these methods having less application for nuclear medicine than the methods that produce true carrier-free isotopes.

However, one can produce carrier-free chemical compounds using reactions of the type $^{12}C(\gamma, n)^{11}C$, and so both cyclotrons and electron accelerators can be used for their production. Much has been written in the chemical literature concerning reactions of atomic species produced by nuclear processes as "hot atom" or "recoil" reactions, and two excellent reviews have been written on this subject.[10,11] Here it will suffice to give one or two simple examples of the type of reaction we are discussing.

If simple hydrocarbons containing 4.5% oxygen are irradi-

TABLE 1.—NUCLEAR REACTIONS FOR THE PRODUCTION OF CARBON-11

Reaction	$^{10}B(d, n)^{11}C$	$^{14}N(p, \alpha)^{11}C$	$^{12}C(^{3}_{2}He, \alpha)^{11}C$	$^{12}C(n, 2n)^{11}C$	$^{12}C(p, pn)^{11}C$	$^{12}C(\gamma, n)^{11}C$
Energy Required	> 6 Mev	7 Mev	≃ 10 Mev	> 20 Mev	> 40 Mev	> 20 Mev
Machine Required	cyclotron	cyclotron	cyclotron	large cyclotron + target	large cyclotron	electron accelerator 30 Mev minimum energy
Potential ^{11}C Yield	≃ 500 Mc.	≃ 500 Mc.	> 100 Mc.	≃ 6 Mc.	≃ 100 Mc.	≃ 1 curie

TABLE 2.—PRODUCTS FORMED BY REACTION OF CARBON-11 WITH SIMPLE HYDROCARBONS

PRODUCT TARGET	PROPANE	CYCLOPROPANE	METHANE
^{11}CO	20.0	11.0	27.0
$^{11}CH_4$	0.3	—	0.1
$^{11}CH \equiv CH$	25.0	50.0	30.0
$^{11}CH = CH$	12.8	2.8	32.0
Propane	—	—	1.7
Propene	6.0	—	1.5
Butenes	3.5	—	—
Butadiene	—	7.0	—

ated in a manner that produces carbon-11 from carbon-12, the major products that are formed by the reaction of the carbon atoms with a few hydrocarbons are shown in Table 2. It is seen that by using different gas phase targets, carrier-free carbon monoxide, carrier-free acetylene and carrier-free ethylene can be formed in high yields. Carbon-11 labeled carbon monoxide has already been shown to be useful in nuclear medicine,[12] ethylene can be used as an intermediate in carbon-11 preparations and acetylene is of great potential for synthetic purposes. Recoil reactions starting with the $^{14}N(p, \alpha)^{11}C$ process can also be used to prepare potentially useful chemicals. Ache and Wolf[13] showed that if nitrogen containing 0.25% of hydrogen was proton irradiated, 35% of the carbon atoms formed $H^{11}CN$, whereas if the nitrogen contained 0.1% of ethane, 55% of the carbon atoms reacted to form $H^{11}CN$. The labeled cyanide can be used for preparing more complex compounds, as will be discussed later. Although cyanide is probably the most useful compound that can be formed using the $^{14}N(p, \alpha)^{11}C$ process, irradiation of nitrogen-oxygen mixtures will form carbon-11 monoxide and dioxide, and nitrogen-hydrocarbon mixtures will give labeled acetylene and ethylene. Recoil reactions have shown little potential for high specific activity labeling of the irradiated material. As has just been shown, the parent compound is labeled with only a small fraction of the isotope; however, more parent compound is formed from liquid or solid targets than from the gaseous targets, and in aromatic targets such as benzene up to 5% of the label appears in the parent compound.[14] However, if the irradiated compound has low radiation sensitivity, it should be possible using fast chromatographic technics to isolate small amounts of low specific activity labeled compounds by direct

recoil labeling. Wolf and co-workers[15] at Brookhaven National Laboratory have prepared labeled dopa by this method, and this compound should have great potential in studying Parkinson's disease.[16]

Although, as has just been demonstrated, the reactions of the type $^{12}C(p, pn)^{11}C$, $^{12}C(\gamma, n)^{11}C$, $^{12}C(^{3}_{2}He, \alpha)^{11}C$, and $^{14}N(p, \alpha)^{11}C$ can be used to form carrier-free carbon-11 labeled compounds, cyclotron reactions using low energy deuterons have been mainly used for nuclear medicine purposes. To date only very simple inorganic compounds labeled with the short-lived isotopes[17,18] have been prepared for in vivo tracer studies. These compounds are oxygen-15 labeled oxygen, carbon monoxide and water; carbon-11 labeled carbon-monoxide and dioxide; and nitrogen-13 labeled nitrogen.

Using very simple chemical technics these compounds can be prepared in high yields, and preparations will be discussed briefly.

Oxygen-15 is produced by a small cyclotron by the $^{14}N(d, n)^{15}O$ reaction. If one could irradiate 100% pure nitrogen, the only reactions that would be possible are

$$^{15}O + N_2 \longrightarrow N_2{}^{15}O$$
$$^{15}O + N_2 \longrightarrow N^{15}O + N.$$

It is impossible, however, to obtain completely pure nitrogen, and when commercially obtained nitrogen is irradiated the main reaction observed is

$$^{15}O + O_2 \longrightarrow O^{15}O + O.$$

As one is trying to prepare oxygen-15 labeled oxygen with little oxygen carrier, it is very fortunate that the reactivity of oxygen atoms with oxygen molecules is very much greater than with nitrogen molecules. $O^{15}O$ labeled in this way can be dissolved in blood which can be reinjected into subjects at a specific activity of greater than 1 mc./cc.

The $O^{15}O$ can be converted easily into either oxygen-15 labeled carbon monoxide or dioxide by circulating the irradiated gas through a heated tube containing activated charcoal. $C^{15}O$ is produced at temperatures above 850 C. and $C^{15}O_2$ at about 450 C. The $C^{15}O$ can be used as a red blood cell tag, and activities of >1 mc./cc. can be obtained. Before dissolving the carbon monoxide the gas should be passed through a soda lime

trap to remove the last traces of the much more soluble carbon dioxide.

If oxygen-15 labeled carbon dioxide is dissolved in water, the label can exchange with the oxygen in the water by the following series of reactions

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \rightleftharpoons OH^- + CO_2.$$

As there are many more water molecules present than carbon dioxide, eventually all of the label will be $H_2{}^{15}O$. It can be shown that after a few minutes all the label is in the form of $H_2{}^{15}O$ when $C^{15}O_2$ is dissolved in distilled water; if $C^{15}O_2$ is dissolved in blood the reaction is still faster due to the enzymatic reaction

$$CO_2 + H_2O \underset{\text{anhydrase}}{\overset{\text{carbonic}}{\rightleftharpoons}} H_2CO_3.$$

By dissolving oxygen-15 labeled carbon dioxide in blood, activities of 10 mc./cc. can easily be obtained. As soon as labeling ceases, the product has been shown to contain more than 99.9% $H_2{}^{15}O$.[19] Labeled water has been advocated as an ideal agent for washout studies[20] and should also be of use for studying body water pools.

Although a useful series of compounds has been labeled with 2-minute half-life oxygen-15, nitrogen-13 labeled nitrogen used for pulmonary studies is the only compound containing ^{13}N to have been prepared for medical studies.[17]

Very little is known of the chemistry of nitrogen-13, and in most of the published work the nitrogen was produced by the $^{14}N(\gamma, n)^{13}N$ reaction.[21] If, however, ^{13}N is produced by the $^{12}C(d, n)^{13}N$ reaction using carbon monoxide or dioxide containing a trace of nitrogen, the ^{13}N reacts preferentially with the trace of nitrogen.[19,22] However, it appears that the molecular nitrogen so formed is in an excited state and may react again, the two major products observed being labeled nitrogen and nitrous oxide (Table 3). The reactions taking place are probably

$$^{13}N + N_2 \longrightarrow N^{13}N^* + N$$
$$N^{13}N^* + XO \longrightarrow N^{13}NO + X$$
$$N^{13}N^* \longrightarrow N^{13}N$$

where XO represents either oxygen, carbon monoxide or carbon dioxide, and $N^{13}N^*$ represents an excited species.

TABLE 3.—PRODUCTS FORMED BY REACTION OF NITROGEN-13

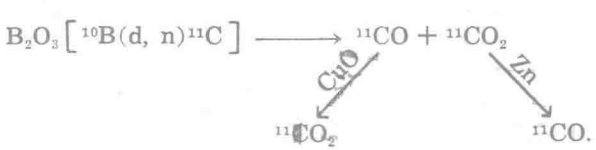
SAMPLE (+ TRACE N_2)	% N_2	% N_2O
100% CO_2	47.5	52.5
100% CO	55.0	45.0
95% CO_2 5% O_2	41.2	58.8
50% CO_2 50% O_2	38.4	61.6

Nitrous oxide, a compound with obvious uses in inert gas washout studies and not easy to prepare by conventional means, can be prepared very simply by the recoil method. There is, however, a technical problem—at high dose rates the nitrous oxide itself is decomposed. Therefore, to prepare ^{13}NNO in high yields (> 150 μc.), it is necessary to devise a flow system with a fast method of separating the nitrous oxide from the irradiated gas.

Very high yields of $N^{13}N$ can be prepared by irradiating carbon dioxide at high dose rates where the nitrous oxide is decomposed and the carrier carbon dioxide absorbed on soda lime.

As we have just discussed, ^{15}O and ^{13}N have several uses as biomedical tracers. However, due to the longer half-life and the importance of carbon, the isotope of the greatest potential in nuclear medicine is probably carbon-11.

Using the deuteron beam of a small medical cyclotron, carbon-11 labeled carbon monoxide and dioxide can be prepared by the irradiation of boric oxide, the beam melting the solid target liberating carbon-11 as carbon monoxide which is radiolytically oxidized to dioxide. One hundred per cent of either oxide can be produced either by oxidation with copper oxide or reduction with zinc



Using this technic the amount of oxide formed is sufficient for studies using the oxides. However, with the use of boric oxide enriched in boron-10 it is possible to prepare 0.5-1 curie of