61. *Radioiodine, I^{125}.* William G. Myers and Han C. Vanderleeden, (The Ohio State University Health Center, Columbus).

Radioiodine, I^{125} ($t^{1/2}=60$ days) is the longest-lived radioisotope obtainable in specific activity suitable for an *in vivo* tracer of stable Iodine, I^{127}. Each 100 disintegrations is accompanied by 142 "usable" photons: about 8 are unconverted 35.4 Kev γ-rays and 134 are 27.3 Kev X-rays following electron capture and internal conversion.

Broad-beam half-thickness in cheese slices is 2.4 centimeters. Calculated narrow-beam half-thicknesses are: Water, 1.6; Sodium Iodide, 0.018; Copper, 0.0054; and Lead, 0.0015 Cm. A 2-millimeter NaI crystal absorbs more than 99 percent of the photons, and the background is quite low. One millimeter of copper or lead absorbs almost all photons so that shielding is simple, collimators can be light, and directionality is readily achievable.

I^{125} is obtained by the bombardment of tellurium or antimony in a cyclotron. Presumably the wasteful waiting for I^{124} and I^{126} to die away can be largely eliminated when we can bombard enriched tellurium targets, or by the $Sb^{123}(He^3,n)I^{125}$ reaction. Present cost is compensated partly by the greatly reduced frequencies of labeling procedures and shipping.

Because there are no high-energy β-particles, radiation exposure for a given initial count rate during complete decay of I^{125} in the thyroid gland will be only about 60 percent of that from I^{131}. Also, the rate of exposure will be seven to eight times slower. Lightness of detector makes readily feasible the continuous recording of accumulation rates. A hard γ-isotope may be used for a second uptake study by easily filtering or "tuning" out the I^{125} photon.

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Radioiodine-125 in Biomedicine: 1959–1984

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Our interest in the "neutron-deficient" radionuclides, I-125 and I-123, initially stemmed largely from a conversation with an official from the Atomic Energy Commission. In the spring of 1957, a meeting in Washington of the Governors of the States was convened to discuss how the AEC and the states might foster and control some civilian aspects of atomic energy. Since the Governor of Ohio was unable to attend, I was privileged to represent him.

During the meetings, we emphasized repeatedly that regulation of the practice of medicine *in all aspects* is a prerogative of the states and not of any branch of the federal government. Our position was that since such regulation is not mentioned in the U.S. Constitution, the Tenth Amendment thereto delegates such regulation to the states, for ... "The powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved to the States respectively, or to the people." We argued, therefore, that the licensure of radionuclides for medical purposes by the AEC would be unconstitutional—the "states-rights" position seemed to be supported enthusiastically by most of the governors present. We pointed out additionally that such proposed licensing by an agency of the federal government would be unique, since the respective states license the practice of medicine *in all other aspects*, in accordance with their constitutional prerogatives. Our position on this proposed regulation was not well received by many attendees. I felt that there must be *some* potentially useful radionuclides

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that would not be controlled because they were not generated . . . "incidental to nuclear fission."

The most commonly used radionuclide in medicine at that time was I-131, produced by nuclear fission. There were two cyclotron-produced "neutron-deficient" radioactive isotopes of iodine, I-125 by two neutrons and I-123 by four neutrons (relative to I-127); thus, it seemed likely that neither of these radionuclides would be subject to control under the premise of "incidental nuclear fission." We recognized that the low energies of the 27.2 and 35.4 keV I-125 photons would necessitate the fashioning of a special energy discriminator for studies with them. In 1957, Mr. Vanderleeden from The Netherlands, who was pursuing postgraduate work in medical physics with us, collaborated with a professor in our physics department to build the necessary instrumentation that would become central to these studies with I-125.

A supplier of cyclotron-generated radionuclides bombarded natural tellurium with 15 MeV deuterons and provided the separated radioiodines. Since eight stable nuclides comprise tellurium, the batch lots contained such contaminants as 8-day I-131, 13-day I-126, and others that emitted "hard" gamma photons; however, 60-day I-125, was the longest-lived among them. Thus, we simply exploited "purification by aging"—storing the material for a few months until the penetrating gammas had largely disappeared.

Results of the preliminary findings and calculations were published in a brief paper in the April, 1960, issue of the *new Journal of Nuclear Medicine* (see page 1389 this issue). In this report we implied that iodine-125 would necessarily be generated with a positive-ion accelerator, such as a cyclotron. In a more detailed paper, "Radioiodine-125," (Volume 1, Number 3, July 1960 issue), it was projected that the results of calculations based upon meager data in the literature indicated that I-125 could be generated in the sequence:

$$^{124}\mathrm{Xe} \xrightarrow[100\ \mathrm{b}]{n,\gamma} {}^{125}\mathrm{Xe} \xrightarrow[17\ \mathrm{hr}]{\mathrm{EC}} {}^{125}\mathrm{I}$$

Even though the abundance of Xe-124 is only 0.096%, the high neutron cross section of about 100 barns would seem to make this method feasible for generation of I-125 in a nuclear reactor. Although these calculations indicated that I-125 could be produced by fission (under AEC regulations), this disadvantage was partially compensated for by the estimate that the costs of production would be of the order of less than about one dollar per millicurie! These projections have been borne out; and, indeed, I-125 has been generated in nuclear reactors since mid 1960.

RADIOIMMUNOASSAY AND RADIOIODINE-125

In view of the physical and economic parameters of I-125 it seemed that this radionuclide might be profitably used in radioimmunoassay (RIA). After this thought was communicated to Dr. Rosalyn Yalow in 1960, she replied, "Your remark about I^{125} is appreciated . . . The use of I^{125} would appear to offer many advantages for labeled proteins, assuming their stability can be assured during the effective lifetime of the isotope." In her tutorial lecture at the annual meeting of The Society in 1976, Dr. Yalow observed that the advantages stemming from the 60-day half-life of I-125 (compared with that of 8-day I-131) contributed to the rapid expansion of RIA. Because of widespread applications of radioiodine-125 in radioimmunoassay, this radionuclide now has been used in biomedicine several times more frequently than all other radionuclides combined.

OTHER SUBSTANCES BEARING IODINE-125

Species-specific immunoglobulins and fragments, labeled with I-125, now are available commercially. They are useful for immunological screening, such as in investigations with monoclonal antibodies. DNA studies are being pursued in many laboratories by means of iodine-substituted nucleosides that "carry" radioiodine-125, and 5-[^{125}I]iodo-2′-deoxyuridine and 5-[^{125}I]iododeoxycytidine are also available commercially.

It has been found that the low-energy Auger and conversion electrons of I-125, as well as its numerous Coster-Kronig transitions, lead to the high specific ionizations that are especially radiotoxic when "carriers" of I-125 become incorporated into DNA. This has led to the design of experiments with I-125 UdR to explore its potential for the internal radiotherapy of tumors.

HIGH-RESOLUTION AUTORADIOGRAPHY WITH IODINE-125

In 1960 it was pointed out that the low energies of the electrons resulting from the decay of I-125 should facilitate the making of autoradiograms having especially high resolution. This prediction was fulfilled within a few years in several laboratories when the histological locations of I-125 atoms in the thyroid glands of animals were demonstrated readily by means of electron ultramicroscopic autoradiography.

RADIATION SOURCES OF IODINE-125

Professeur Bernard Pierquin, Radiologiste des Hopitaux de Paris, first suggested in 1960 that the physical properties of I-125 should be applicable advantageously for interstitial radiation therapy. In a 1964 report we proposed that permanently implanted or removable sources of I-125 would lead to lowered radiation exposures to personnel handling them, to greatly decreased megagram-rads of exposure to the patient, and that there would be significant shielding of bone marrow from sources placed near bone. Since then, "seeds" loaded with I-125 have become available. Expanding applications for their placement in cancers now are occurring, especially at centers such as The Memorial Sloan-Kettering Cancer Center in New York City, as well as in many other institutions where cancers are commonly treated by radiation applied interstitially.

A radiograph of a cadaver hand that had been made with a small source of I-125 photons located above it was shown in an article in 1962. The photoelectric absorption of the 27.2 keV and 35.4 keV photons by bone resulted in excellent resolution. Details of soft tissues were revealed well also, chiefly because of the predominant all-or-none photoelectric absorption of them by water, and the resulting decreased Compton scattering. Recently, a low intensity x-ray imaging device has become available. Hundreds of millicuries of I-125 within the unit approximate a point source of 27.2 and 35.4 keV photons. When the trigger of this light-weight, hand-held instrument is pulled, the I-125 source swings into the "on" position. A clever battery-powered image-intensifier device, which was developed at NASA's Goddard Space Flight Center, "sees" the I-125 photons. Interposing a wrist, hand, ankle, or foot makes it possible to differentiate quickly between fractures and sprains. Applications in sports medicine are obvious as well as in the operating room to aid in the positioning of pins, screws, and wires.

From a relatively inauspicious beginning, iodine-125 has become one of our most important radioactive elements. This radionuclide has contributed extensively to the entire gamut of medicine—research, clinical diagnosis, and therapy.

[*Editor's Note:*

Although Bill Myers' original article on I-125 was published as an abstract, the content summarized well the salient information available in 1960. Bill has lauded brevity, as exemplified by the very brief report of F. Joliot and I. Curie that appeared in *Nature* in 1934, for which work they received the Nobel Prize.

Bill Myers, a charter member of our Society, is one of our most distinguished scientists and able teachers. As a student of his many years ago, I have warm memories of his fascinating lectures and gratefully acknowledge my debt to him for provoking my interest in radioisotopes. Over the last ten years it has been entertaining and instructive to work with Bill in his role as Historian, since he personally knew so many eminent scientists who have contributed to our field. I have enjoyed immensely his recounting incidents related to various discoveries in nuclear medicine. An organization is truly obligated to a member who assiduously stores the relevant historical information vital to the future, for in any area of endeavor, historical knowledge contributes to current perspective.]