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Technetium-99m: The Early Days

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It is a great honor for me to have been invited to participate in this Symposium and to share my recollections of the early days of technetium-99m in nuclear medicine. I would like to thank the University, the CNR, and the Symposium Steering and Organizing Committee for inviting me.

About 1950, shortly after the start-up of Brookhaven National Laboratory on Long Island, New York, a facility was built called the Hot Laboratory and an organization was established known as the Hot Laboratory Division to do research and development on fission product separation and the development of applications for fission products. This was done at the suggestion of the late Warren Winsche, who was in charge of organizing this division. One of the first projects to be looked at was the potential application of the separation of short-lived isotopes from longer-lived parent isotopes or the development of "radionuclide generators".

One of the first systems to be studied was the separation of short-lived iodine-132 from its 77-hour parent, tellurium-132. The Hot Laboratory Division at that time was headed by L. G. Stang and the radioisotope development work was headed by Walter Tucker. A simple system was developed whereby tellurium-132 was separated from the other fission products and was then adsorbed on a simple alumina column; the daughter, iodine-132, was eluted from the column with a chemical reagent, in this case dilute ammonium hydroxide. The use of iodine in medicine was well known, and it

was thought that a short-lived iodine radioisotope would be useful in medical studies. Studies being carried out to improve the purity of the eluted iodine-132 resulted in the detection of a trace contaminant which proved to be technetium-99m. It was then realized that the technetium was coming from its parent, molybdenum-99, which was following the chemistry of tellurium in the separation process for other fission products. Similarities between the chemistry of the tellurium-iodine parent-daughter pair and the molybdenum-technetium pair led to the development of the molybdenum-99-technetium-99m generator system.

As a result of this discovery, a technetium-99m generator was developed primarily by Walter Tucker and Margaret Greene of the Brookhaven Hot Laboratory Division. This and other related work was reported at a meeting of the American Nuclear Society held in Los Angeles, California, in June 1958 (1,2). The original generator is shown in Figure 1 and is essentially the same, physically, and similar chemically to the iodine-132 generator. At about the time of the development of this generator, I was placed in charge of radioisotope production which included both the production of the generators and their continued development.

It turned out that most of the radionuclides under investigation at Brookhaven were primarily of medical interest and for this reason both Tucker and I started going to nuclear medicine meetings to promote our developments and also to find out what the needs of the field were. At about this time, Tucker was transferred out of this field and I continued this line of work

alone. It soon became obvious that technetium-99m possessed ideal physical properties for many of the diagnostic procedures used in nuclear medicine, and several years were spent in trying to interest the medical profession in evaluating this radionuclide without much success. In the meantime, several generators, both iodine and technetium, were supplied to industry for developmental work of various types such as in studies of mixing efficiency where the short half-life allowed the use of the radionuclide tracer directly in the process.

The first medical researcher (early 1960's) to use technetium-99m was Dr. Claire Shellabarger of the Brookhaven Medical Department. While studying thyroid physiology with different radionuclides, he observed the localization of technetium-99m in thyroid tissue. This fact went unnoticed as he shortly thereafter left the Laboratory.

It was just 29 years ago in June of 1960 here in Italy, in Rome, that I presented a paper which was also published in the Transactions of the 7th International Electronic and Nuclear Symposium (3) (Fig. 2). This paper described a number of radionuclides under development at Brookhaven and included the method of production of the technetium-99m generator and the parent, fission product molybdenum-99, and mentioned the ideal physical properties of technetium-99m for medical applications. While flying to attend this meeting, I met Dr. Paul V. Harper of the University of Chicago and the Argonne Cancer Research Hospital. I spent considerable time extolling the merits of

technetium to him. Apparently, the message did not get across because nothing was heard from Harper until October 1961. That is when Dr. Harper ordered the first of many generators from Brookhaven initially for use in making blood flow measurements due to the ability to get high count rates with technetium-99m because of the low radiation dose. During initial studies, he detected the rapid uptake of technetium-99m in the thyroid gland and this was followed by the observation that it localized in brain tumors. These studies created an interest in technetium-99m generators at a number of other institutions and the growth of technetium was under way. During the first five years all of the technetium-99m generators were produced and distributed by Brookhaven National Laboratory.

During this period a number of improvements were made in the generator to lower the contamination levels. Elution of the generator with more biologically compatible reagents and increasing the amount of activity that could be eluted greatly facilitated the usefulness of technetium-99m. During this period extensive work was also started on the development of new radiopharmaceuticals labeled with technetium-99m at Brookhaven, Argonne Cancer Research Hospital, and other institutions in an attempt to make the radionuclide more widely useful.

Early in the 1960's a joint collaborative program was set up between my program at Brookhaven and with Dr. Paul Harper and Katherine Lathrop at the University of Chicago. The purpose of this work was to try to develop biologically useful tracers

labeled with technetium-99m. Results of this effort included the development of a solvent extraction procedure which was useful in purifying technetium which was eluted from the generator, preparation of the first reduced compounds of technetium-99m, early work on the development of technetium-99m-labeled human serum albumin, and the development of the first technetium-99m-labeled sulfur colloid. I later adapted the solvent extraction technique for separating technetium from its parent, molybdenum, for use in producing medically useful quantities of technetium-99m from molybdenum-99 produced by the bombardment of molybdenum oxide in low flux research reactors. This system proved useful in developing countries until generators became generally available in the late 1960's. I assisted the Turkish and Greek nuclear research centers in setting up systems which supplied them with technetium for nuclear medicine programs for several years (4).

The development of technetium-99m labeled sulfur colloid is a good example of how simple it was in the early days in terms of how rapidly a new radiopharmaceutical could be developed. One of the first things that our collaborative effort with the University of Chicago suggested was, that a useful radiopharmaceutical would be a colloid labeled with technetium-99m. Working at Brookhaven, we tried to carry technetium on a number of colloids and found out that colloidal molybdenum seemed to be the most satisfactory. The colloid was prepared by bubbling hydrogen sulfide through an acid solution containing small amounts of molybdenum carrier. When this was carried out in the presence of gelatin as a stabilizer, stable

colloids were formed. One time we tried bubbling H_2S through an acid solution of pertechnetate in the presence of gelatin and, to our surprise, the activity was removed by a very fine millipore filter. Filtration studies of this colloid using different porosity millipore filters indicated that the colloid size appeared to be in the useful range with the activity carried on colloidal particles of sulfur. I then called our collaborators in Chicago and reported our success with forming the technetium-labeled colloid and told them how to prepare the material. The next day they prepared a batch of the colloid and then injected it into a mouse and imaged the mouse with their small animal rectilinear scanner. As a result, they got excellent images of the mouse liver. That same afternoon, using a new batch of the technetium colloid, they did a scan on a patient and reported back to us that the colloid exceeded all expectations and thus a new and very important radiopharmaceutical was developed, a far cry from what is involved in such a development today (5)!

From the very earliest days of technetium-99m, I was interested in the possibility of labeling red blood cells with technetium. We knew that red cells could be labeled with chromium activity with the chromium in the anionic form as chromate ion. In our naivete, we therefore thought that we should try to label red cells with technetium due to the fact that technetium was also in an anionic form as pertechnetate. Unfortunately, as pertechnetate is fairly stable, it readily washed into the cells but also just as readily washed back out. As more knowledge of the chemistry of

technetium was developed, we were finally able to label red cells with technetium using stannous tin to reduce the technetium within the red cells and, therefore, prevent it from washing out of the cells. In 1976, a simple kit was developed for labeling a patient's red blood cells, which made the procedure easy to use in medical centers all over the country (6). This procedure required the separation of red blood cells from other components of blood. More recently, a new version of the kit has been developed at Brookhaven which allows the quantitative labeling of red cells with technetium-99m in whole blood thereby greatly simplifying the procedure (7,8). Preliminary human studies using this method will be presented at this meeting.

The technetium-99m research and development program was greatly enhanced in 1964 with the arrival of Dr. Harold L. Atkins at Brookhaven and the starting of a clinical nuclear medicine program. As a result of this collaboration, many new developments were made including the first high-efficiency, low-energy focusing collimator for rectilinear scanning with technetium (9), evaluation of the first technetium-99m-labeled chelate, DTPA, for kidney studies (10), the first instant kit for the preparation of technetium-99m-labeled DTPA using stannous tin for the reduction of technetium-99m (11), resolution of problems associated with the use of tin (12), and the use of gel filtration for quality control of technetium-99m-labeled radiopharmaceuticals (10).

The number of institutions using the technetium generator grew rapidly from 1963 until 1965. In 1966, Brookhaven withdrew

from the production and distribution of technetium-99m generators in favor of commercial distributors. Up until that time, we supplied approximately 1500 generators ranging in size from 50 millicuries to 400 millicuries each. The earliest commercial generators, based on the neutron irradiation of stable molybdenum-98 for the production of molybdenum-99 were developed and distributed by Nuclear Consultants, Inc., St. Louis (later taken over by Mallinckrodt) and Union Carbide Nuclear Corporation, New York. A major advance during this period was the development of the sterile enclosed generator by Squibb.

The rapid growth of generator production has continued over the years with the next major change being the general return to fission-product molybdenum-99 generators. This was a return to the original type of Brookhaven generator.

The impact of the technetium generator and technetium radiopharmaceuticals on nuclear medicine is evident from the fact that for many years over 80% of the procedures in nuclear medicine have involved the use of technetium-99m and the dollar value of the commercial aspects of technetium in the U.S. alone has been estimated to be over two billion dollars. The popularity of technetium-99m in nuclear medicine continues despite numerous predictions of its demise over the last 15 years, particularly with the development of each new modality in the field. First, it was thought that a new and better isotope would come along to take its place, CAT scanning would take its role in many applications, and then PET would replace it. However, research and development resulting in new technetium radiopharmaceuticals (13-15) and

improved equipment have always increased the use of technetium. The future continues to look bright with the widespread use of SPECT and the synthesis of new compounds by inorganic chemists. You will hear about many such new and exciting developments at this meeting, I am sure.

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References

(1) Richards, P., Tucker, W. D., and Srivastava, S.C. Technetium-99m: An historical perspective. Int. J. Appl. Radiat. Isot. 33, 1982, 793-799.

(2) Tucker, W. D., Greene, M. W., Weiss, A. J., and Murenhoff, A. P. Methods of preparation of some carrier-free radioisotopes involving sorption on alumina. BNL 3746. American Nuclear Society Annual Meeting, Los Angeles, CA, June 1958. Trans. Am. Nucl. Soc. 1, 1958, 160.

(3) Richards, P. A survey of the production at Brookhaven National Laboratory of radioisotopes for medical research. VII Rassegna Internazionale Elettronica e Nucleare, Roma, June, 1960. Atti Officiale, pp. 223-244.

(4) Richards, P. ^{99m}Tc: An inexpensive route to a versatile radioisotope, Radiation and Isotope Technology in Latin American Development, Proc. of ANS Topical Mtg., San Juan, PR, May 4-6, 1969, PRNC 135, 1969, pp. 252-260.

(5) Harper, P. V., Lathrop, K., and Richards, P. A radiocolloid of ^{99m}Tc. J. Nucl. Med. 5, 1964, 382 (abstr.).

(6) Smith, T. D. and Richards, P. A simple kit for the preparation of ^{99m}Tc-labeled red blood cells. J. Nucl. Med. 17, 1976, 126-132.

(7) Srivastava, S.C. and Chervu, L.R. Radionuclide-labeled red blood cells: Current status and future prospects. Semin. Nucl. Med. 14, 1984, 68-82.

(8) Srivastava, S. C., Straub, R. F., Meinken, G. E., and Gil, M.C. Current state-of-the-art of blood cell labeling, Current Applications in Radiopharmacology, Billinghurst, M. W. (ed.), Pergamon, New York, 1986, pp. 166-183.

(9) Richards, P. and Atkins, H. L. A collimator system for scanning at low energies. J. Nucl. Med. 8, 1967, 142-152.

(10) Richards, P. and Atkins, H. L. ^{99m}Technetium labeled compounds. (Proc. 7th Annual Mtg. Jpn. Soc. Nucl. Med., November 1967, Tokyo, Japan), Jpn. Nucl. Med. 7, 1968, 165.

(11) Eckelman, W. C. and Richards, P. Instant ^{99m}Tc-DTPA. J. Nucl. Med. 11, 1970, 761.

(12) Srivastava, S.C., Meinken, G., Smith, T. D., and Richards, P. Problems associated with stannous ^{99m}Tc-radiopharmaceuticals. Int. J. Appl. Radiat. Isot. 28, 1977, 83-95.

(13) Srivastava, S. C. and Richards, P. Technetium labeled compounds. Radiotracers in Biology and Medicine, Rayudu, G.V.S. (ed.), CRC Press, Boca Raton, Florida, 1983, pp. 107-185.

(14) Deutsch, E.A., Libson, K., Jurisson, S., and Lindoy, L.F. Technetium chemistry and technetium radiopharmaceuticals. Progr. Inorg. Chem. 30, 1983, 75-139.

(15) Clarke, M. J. and Podbielski, L. Medical diagnostic imaging with complexes of ^{99m}Tc. Coord. Chem. Rev. 78, 1987, 253-331.

Legends for Figures

Figure 1. The original Brookhaven ^{99m}Tc generator (shown without shielding), ca. 1958.

Figure 2. U.S. Delegation to 5th Nuclear Congress, Rome, Italy, outside the American Embassy. Pictured from left to right are: (1) Dr. R. F. Schilling, delegation chief; (2) Dr. Donald Van Dyke, Donner Laboratory; (6) Dr. Harold Rossi, Columbia University; (7) Dr. John Gillette, Oak Ridge National Laboratory; (8) Dr. Paul Harper, Argonne Cancer Research Hospital. (Photo by author).