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THE PRODUCTION AND ISOLATION OF ASTATINE-211 FOR BIOLOGICAL STUDIES

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In recent years, astatine -- the heaviest of the halogen group -- has become a valuable tool in the study of thyroid physiology. Astatine was first isolated by Corson et al.<sup>1</sup> and later by Johnson et al.,<sup>2</sup> who distilled the astatine from a bismuth target and collected it in a glass U-tube containing a few drops of concentrated nitric acid. Garrison et al.<sup>3</sup> developed a method for the preparation of astatine solutions suitable for intravenous injection which eliminated the high salt concentrations and adjustment of pH. Believing that there will be increased interest in the use of At<sup>211</sup> on the part of biologists and medical researchers, we present here in detail the method of Garrison for the preparation of At<sup>211</sup>, with more recent modifications of the method.

Hamilton et al.<sup>4</sup> reported that the temperature at which the astatine was distilled from the bismuth target was about 425°C. At this temperature, the total yield at the conclusion of a bombardment was approximately 25 μc/μah. For animal experiments at lethal levels<sup>5</sup> greater yields of activity were required. An increase in distilling temperature was found to produce more than 150 μc/μah at the conclusion of the bombardment.

In early studies using material prepared at higher temperatures,<sup>6</sup> it was found that the liver uptakes were greater than those reported by Hamilton et al.<sup>4</sup> Histological sections of liver taken from a rat that had survived after receiving 1.8 μc/g of At<sup>211</sup> intravenously showed severe damage in small areas which were surrounded by relatively normal tissue.<sup>7</sup> These At<sup>211</sup> solutions also showed a definite Tyndall effect. Radioautographs on NTA film\* were prepared from sections of liver and spleen and bone marrow smears from rats that had received 50 μc of the "high temperature" At<sup>211</sup> preparation intravenously. The radioautographs showed "stars" of alpha tracks<sup>6</sup> -- suggesting adsorption of At<sup>211</sup> atoms on some colloidal material -- rather than scattered single tracks as would be normally expected, and brought out a possible explanation of the spotty damage previously seen in the liver, a relatively radioresistant organ.

A solution of At<sup>211</sup> to be used for injection was centrifuged for 30 minutes at 5,000 g on an International centrifuge, size 2, model V. There was no apparent change in particle suspension as determined either radioautographically

\* Eastman's NTA Autoradiographic stripping film.

or by examination for Tyndall effect. A second solution of  $\text{At}^{211}$  was prepared and subjected to centrifugation for 30 minutes at 35,000 rpm or an average of 80,730 g, on a Spinco model L ultracentrifuge with No. 40 head.\* Under these conditions, more than 50% of the activity remained in the centrifuge cone, as indicated by monitoring before and after removal of the solution from the cone. On longer ultracentrifugation at the same speed, no further loss was incurred. Alpha-particle stars were entirely absent in radioautographs prepared from animals that received this solution intravenously.<sup>7</sup>

Samples of the residue washed from the cone with strong acid were analyzed spectrographically and the following elements were present: aluminum, silicon, beryllium, and bismuth, probably in the form of oxides. It was decided that one or possibly all of the elements found spectrographically must be partially involved in the colloid formation. The use of gold instead of aluminum as the back plate for the bismuth target and the replacement of the protective mica liner with a quartz boat reduced the loss of  $\text{At}^{211}$  during centrifugation to approximately 25%.

If the method described in this report is followed closely, it becomes fairly routine, but failure to follow these steps will result in large activity losses.

#### Method

About 220 mg/cm<sup>2</sup> of spectroscopically pure bismuth\*\* is fused to a 10-mil gold disc, 3-3/8 inches in diameter, to conform to the 2-by-7-cm. collimating slot in the cyclotron window assembly, Fig. 1. The beam is sufficiently well collimated so that with centering of the bismuth more than 80% of the gold target may be recovered free of induced radioactivities. Enough platinum foil is placed in the path of the alpha beam at A (Fig. 1) to degrade the alpha-particle energy from the 47 Mev normally produced by the 60-inch cyclotron at the Crocker Laboratory to 29 Mev. This is the optimum energy for the alpha-2n reaction with bismuth to form  $\text{At}^{211}$  without simultaneously producing  $\text{At}^{210}$  by the alpha-3n reaction.<sup>8,\*\*\*</sup>

Air is blown in along the side of the platinum foils to dissipate the heat produced by the beam. One-half atmosphere of helium is held in the area between the foils and the bismuth so that this area will be free of any oxygen. The presence of oxygen would lead to the formation of bismuth oxide, which could be carried over in the distillation operation. Because  $\text{At}^{211}$  is very

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\* Courtesy of the Bio-Organic group under the direction of Dr. Melvin Calvin.

\*\* The bismuth was obtained from Johnson, Matthey and Company, Limited, London E. C. 1. It must be free of antimony, which would produce an iodine contaminant.

\*\*\*  $\text{At}^{210}$  decays to the long-lived  $\text{Po}^{210}$ , which is physically hazardous and would introduce experimental errors in dose calculations.

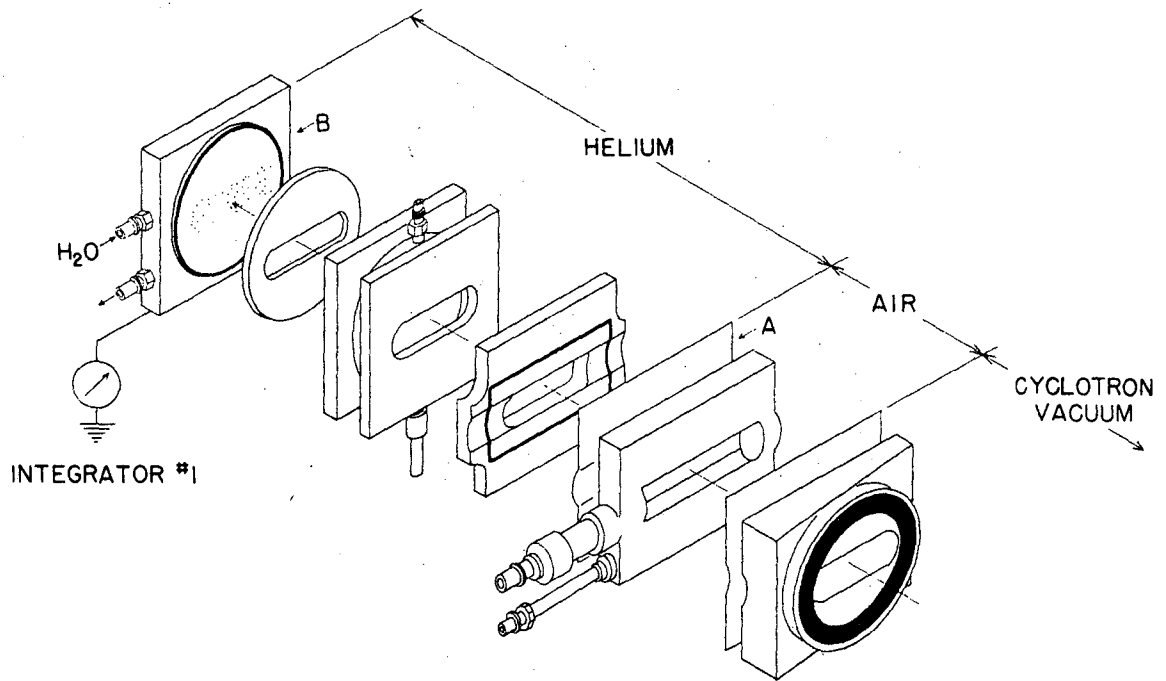


Fig. 1.

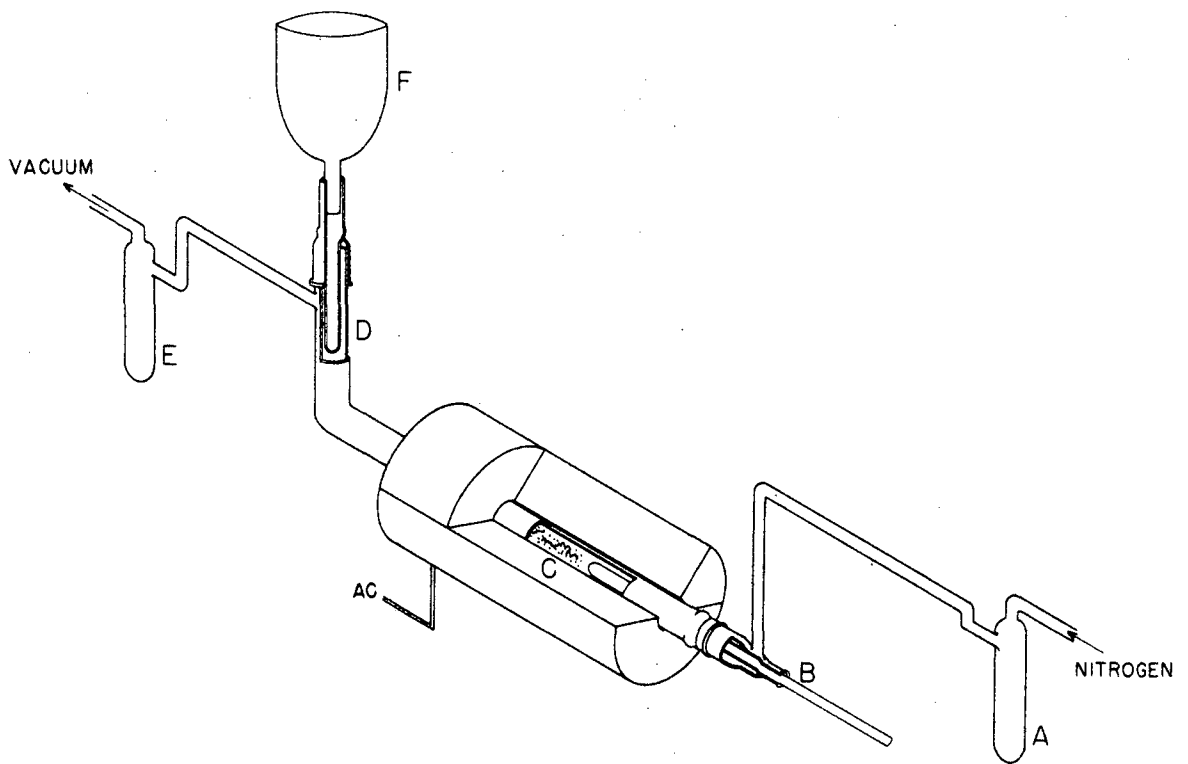
volatile, even at room temperatures, water cooling is carried on just behind the gold target plate at B (Fig. 1). The total beam on the assembly in micro-ampere hours is indicated by the integrator (Fig. 1).

At the end of the bombardment, the target and holder are allowed to cool for a short period of time to permit the decay of the short-lived radioisotopes produced in the aluminum, platinum, and gold foils. The target plate is then removed from the assembly and carefully dried. After the removal of the excess gold from either side of the gold-bismuth alloy, the target is cut lengthwise into two pieces, taking care to avoid flaking of the bismuth. These two pieces are placed in a small quartz boat, which is inserted into the large quartz tube shown at C (Fig. 2). Survey-meter readings are taken at the surface of the heating unit and at the cold finger D (Fig. 2) in order to provide a reference point for later determination of completeness of the distillation of the  $\text{At}^{211}$ . Liquid nitrogen is put in the cold finger reservoir F (Fig. 2) and around the trap E (Fig. 2). In order to facilitate collection and to prevent the adsorption of the astatine on the glass of the cold finger, a thin film of ice is deposited on the finger by soft breathing. The entire system is evacuated with a Cenco-Megavac pump and tested with a Tesla coil. When a vacuum of less than 200 microns is obtained, an inert streaming gas -- helium or nitrogen -- is introduced through the capillary tube between A and B (Fig. 2). Two pounds of pressure is maintained on the tank side in order to permit a steady flow of gas over the bismuth to the cold finger. Neither water nor oxygen is permitted to enter the system, because it has been found that these tend to increase colloid formation.

The furnace is turned on, and the target is brought rapidly to  $700^{\circ}\text{C}$  as determined by a thermometer inserted in B (Fig. 2). Below this temperature the yield of  $\text{At}^{211}$  is low and above it a brown to black layer of bismuth may distill onto the cold finger and cause great loss of activity in centrifugation. The quartz tube between the furnace and the finger is flamed periodically to prevent adsorption of any activity on the walls of the quartz tube. The temperature is held at  $700^{\circ}\text{C}$  for approximately 40 minutes, or until survey-meter readings give no further indication of movement of activity from target to finger.

The furnace is turned off and opened, and the apparatus is allowed to cool to approximately  $100^{\circ}\text{C}$ . The vacuum pump is turned off. When the system has returned to atmospheric pressure, the cold finger is carefully lifted straight up to prevent any of the ice from flaking off. The finger is washed with 10 ml of isotonic saline containing 5 mg/ml of  $\text{Na}_2\text{SO}_3$ . This solution is placed in an ultracentrifuge for 20 minutes at 30,000 rpm. The centrifuge cone is read with a survey meter and the value recorded. The supernatant is transferred to a 25-ml serum bottle. A 10-ml volume of water is added to the cone and shaken with the residue. The cone is again metered to determine the amount of activity remaining in the cone as colloid.





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Fig. 2.

The concentration of  $\text{At}^{211}$  in the solution is measured by diluting 0.25 ml of the original solution to 1,000 ml with 1 N  $\text{NaOH}$  containing 10 mg/ml  $\text{Na}_2\text{SO}_3$ . After thorough shaking, the activity is assayed by the method described by Durbin et al.<sup>9</sup> The decay is followed closely on both the alpha and scintillation counters. This indicates if any contaminants are present in the injection solution.

#### Summary

A method is described in detail for the routine preparation of millicurie amounts of  $\text{At}^{211}$  in a form suitable for animal injection.

#### Acknowledgments

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