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Marie Curie and nuclear medicine: Closure of a circle

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I. INTRODUCTION

This paper describes the relationship between Marie Curie and the emergence of the field of nuclear medicine. Although she did not carry out specific experiments in nuclear medicine much of this story relates to her many personal associations with scientists working in related fields. Intimate details of these interactions have been recorded by de Hevesy and others.[1–7]

Marie Curie's activities and research left her imprint on nuclear medicine, which continues to this day. Much of her impact is related to the role of women in science, biology, and medicine. She successfully overcame struggles for recognition in the first decades of this century. One of her major achievements was the development of field-radiography for wounded soldiers in World War I. Her continued endeavors to provide radium therapy for cancer was a giant step for humanity. She worked unceasingly in the laboratory to separate and identify radioactive elements of the periodic table. The standardization of these elements resulted in the 1931 report of the International Radium-Standards Commission[8] and the posthumous two-volume *Radio-aktivité*.[9]

A few details of her personal life are helpful in understanding the scope of these accomplishments. They also illustrate aspects of Marie Curie, especially her personality, that bear on her contributions to nuclear, medicine. Her ability to recognize what later developed as a major scientific breakthrough while shoveling pitchblende—and maintaining control of her discovery—is unique. Her dissertation led to the awarding of the 1903 Nobel Prize in Physics which she shared with her husband and Henri Becquerel. At the same time, she was both wife to Pierre Curie and mother to Irène and Eve. To quote Marie Curie:[10]

> I have frequently been questioned, especially by women, how I could reconcile family life with a scientific career. Well, it has not been easy; it required a great deal of decision and of self-sacrifice.

This combination of career and family provides a clear model for a life of achievement which conferred great rewards to society.

Pierre's sudden death in 1906, leaving Marie a young, single mother, is a tragic occurrence that has been experienced by many women. She reacts in her own words.[10]

> Crushed by the blow, I did not feel able to face the future. I could not forget, however, what my husband used sometimes to say, that, even deprived of him, I ought to continue my work.

In reading about her daily life as described by her daughter, Eve, it is easy to visualize her direct approach to those circumstances. Her two dresses are black and lacking in ornamentation. Home is austere, meals are simple. Yet the girls were quite well educated and developed as individuals in their own ways—one a scientist, the other a distinguished writer.

This next series of events may seem unrelated to our main topic; however, it describes in a most human way the courage and determination of Marie Curie during and after a series of personally discouraging events which she overcame. In 1910 Marie Curie was encouraged to apply for election to the French Academy of Science, a most prestigious organization that had never had a female member since its inception in 1666. There was considerable public interest about the election process but her application was turned down early in 1911. (The first woman admitted to the Academy 51 years after Marie Curie applied was Marguerite Pery for her discovery of Francium while working in Marie Curie's laboratory.) There were two ballots, with defeat by one vote and then by two votes.

Following the death of her beloved Pierre, Marie Curie continued to experiment, lecture, and maintain a home. Marie and Paul Langevin, a distinguished physicist and close family friend, became involved in an emerging love affair in 1910. This episode is dramatically described by Mme. Borel.[11] Due to disagreements with his wife, Paul Langevin had moved to a separate domicile near the Sorbonne. Jeanne Langevin, his extremely jealous and aggrieved wife, learned of this affair. Madame Langevin then purloined a packet of letters written between Marie and Paul. In November 1911 she released them to a xenophobic and vitriolic Paris press, three days before the announcement of Marie Curie's second Nobel Prize.

Amidst this raging scandal, Marie received notification that she was awarded this second Nobel Prize, this time in Chemistry. At the time she was in Brussels for the first Solvay conference, along with other leading physicists of the time, including Langevin. Svante Arrhenius, Professor of Physics in Stockholm, was a 1903 Nobel Prize winner in Chemistry for his work culminating in the theory of electrolytic dissociation.[12] As a member of the Nobel committee, he had enthusiastically advocated awarding a second Nobel Prize to Marie Curie. Since she considered Arrhenius to be a good friend, she wrote him a letter soliciting his opinion regarding her attendance at the ceremony. In his reply, he reassured her of his support despite the growing press scandal. Subsequently, Arrhenius learned of the duel between Langevin and Thery, the editor of the newspaper that published the letters and a former school comrade of Langevin.[4] Arrhenius then wrote a second letter, suggesting she not accept the Prize because of the Paris scandal. Although Marie had not planned to go to Stockholm for the ceremony, the letter from Arrhenius changed her mind, as she explained in her reply:

> The action which you advise would appear to be a grave error on my part. In fact the prize has been awarded for the discovery of Radium and Polonium. I believe that there is no connection between my scientific work and the facts of private life.[6]

Accompanied by her sister Bronia and her elder daughter Irène, Marie journeyed to Stockholm to receive the Prize in person.

Marie Curie did not live in a vacuum. She actively communicated with fellow scientists in many countries and attended conferences with the great minds in physics who helped shape theories of modern physics. For example, she attended the Solvay Conferences on Physics from its inception in 1911 until the 1933 conference, which took place one year before her death. One important association was with de Hevesy.

II. DE HEVESY

Both Marie Curie and Georg de Hevesy began their careers in radiochemistry. The association between them is particularly intriguing as George de Hevesy is considered to be the father of nuclear medicine.[13] He received his doctorate at Freiburg University in 1908 at the age of 23, and then went to Manchester to learn about electrical conductivity of gases under Ernest Rutherford.[14]

For many impecunious students and scientists, lodging and provender was often found in nearby boarding homes. It was so with de Hevesy. Although satisfied with the lodging and usually with the food, he took exception to one practice, namely serving leftover meat pie, no matter how tasty, several days after the Sunday repast. In his own words, de Hevesy described this event that represented his first foray into what became the field of nuclear medicine.

> The coming Sunday in an unguarded moment I added some (radio)active deposit to the freshly prepared pie and on the following Wednesday, with the aid of an electroscope, I demonstrated to the landlady the presence of the active deposit in the souffle.[3,13]

Coincidentally both Marie Curie and de Hevesy worked with actinium. Initially Rutherford assigned de Hevesy a project on the solubility of actinium emanations in water. Parenthetically, Marie Curie, in her long career, also was intermittently involved in the separation and characterization of actinium.[2] Rutherford next assigned de Hevesy the now anecdotal problem of separating Radium D from stable lead, an attempt that was unsuccessful even after a year. Not known at that time was that Radium D is an isotope of lead and thus chemically inseparable. Brilliantly, de Hevesy realized that lead could be ''spiked'' with Radium D and thus the properties of the lead could be analyzed. This deduction and subsequent experiments served as a next step in the founding of the radiotracer method.

In relating several other anecdotes about de Hevesy, Paul Frame[15] of Oak Ridge National Laboratory describes two studies leading de Hevesy to postulate and later prove that biological systems exist in a dynamic equilibrium. One of the first tracer elements available to de Hevesy was P-32. Using this tracer he initially investigated whether the mineral part of bone was replaced during life. The result showed the ''dynamaticity of phosphorus metabolism.''[3] This was the first study to demonstrate that biological systems exist in a dynamic equilibrium—rather untraditional thinking for the time.

Recently, Gustav Arrhenius, a scientist from La Jolla and a grandson[16] of the chemist Svante Arrhenius, pointed out that St. Thomas Aquinas, some 700 years earlier, had reached the same conclusion, albeit not experimentally.[15] Aquinas ruminated on the reconstitution of a cannibal on the day of resurrection if its reconstituted parts previously belonged to others. Aquinas concluded: ''the identity of the body is not dependent on the persistence of the same material particles,'' ''[that] during life, by the process of eating and digesting, the body undergoes perpetual changes.'' De Hevesy (1962) gives full credit to the saint. Further intertwining, de Hevesy's eldest daughter married Gustav Arrhenius![14]

de Hevesy did not know Pierre Curie personally as the younger man did not begin work in Rutherford's laboratory until 1911. In several accounts de Hevesy describes his interactions with Marie Curie. To quote de Hevesy.[3]

> When passing through Paris on the way to Manchester, I never failed to call on Marie Curie and I was always sure to find her amidst experimental work. She was usually surrounded by several girl assistants precipitating or crystallizing preparations. The only protection that she used was finger caps of rubber. When engaged with the concentration of actinium from rare-earth samples, she generously presented me with an actinium preparation. I consider this specimen one of my most precious belongings. As the years pass by, the bottle containing the radioactive sample is getting more and more coloured, indicating the many years which have elapsed since I met this most remarkable personality and great pioneer.

de Hevesy continues:

> At a later visit to the Institut de (sic) Radium, I met Joliot, who was then a young assistant engaged in the study of the electrochemistry of polonium, which many years earlier was in the center of interest of Paneth and

myself. Also, Irène Curie worked in the laboratory of her mother.

III. BIOLOGICAL EFFECTS

Several early observations in handling the new radioactive substances were reported by Becquerel and Pierre Curie.[10] Both experienced radiation reactions to the forearm and hand, noting erythema, followed by ulceration and delayed healing. Experiments were conducted on animals demonstrating what is now recognized as the acute radiation syndrome as well as late deterministic effects.[10] Unfortunately many of the implications of these experiences were unrecognized, resulting in prolonged disability and also deaths of some laboratory workers. Marie Curie eventually recognized the many late effects of ionizing radiation and cautioned x-ray and radiation workers, yet she did not follow her own advice. French physicians and physicists were involved in the development of international safety policies and practices as early as 1913.[17] However, these recommendations were not rigorously implemented in Marie Curie's laboratory. In particular, Marie Curie appeared quite resistant to consideration of the deleterious effects of radiation.[6]

IV. CANCER

The potential uses of radium to treat cancer were recognized very early. Marie Curie writes in 1923 of the implications of her discovery of radium:[10]

> The first experiments on the biological properties of radium were successfully made in France with samples from our laboratory, while my husband was still living. The results were, at once, encouraging, so that the new branch of medical science, called radiumtherapy (in France, *Curietherapy*), developed rapidly, first in France and later in other countries... The radiumtherapy and the radium production developed conjointly, and the results were more and more important, for the treatment of several diseases, and particularly of cancer.
>
> It may be easily understood how deeply I appreciated the privilege of realizing that our discovery had become a benefit to mankind, not only through its great scientific importance, but also by its power of efficient actions against human suffering and terrible disease. This was indeed a splendid reward for our years of hard toil.

The next step in the evolution toward nuclear medicine occurred within Marie Curie's laboratory. Frédéric and Irene Joliot-Curie discovered artificial radioactivity on January 15, 1934. The specific reaction that was demonstrated was: $10B+4He=13N+{}^{1}n$ (Ref. 9). The 13N decays with the emission of positrons and is commonly used today as a myocardial perfusion agent.[18] Within a short time Marie Curie, Pierre Regaud, and Paul Langevin entered the laboratory and the effect was again demonstrated.[19] Later, Frédéric Joliot recounts that moment:

> I will never forget the expression of intense joy which overtook her when Irène and I showed her the first [artificially produced] radioactive element in a little glass tube. I can see her still taking this little tube of the radioelement, already quite weak, in her radium-damaged fingers. To verify what we were telling her, she brought the Geiger-Muller counter up close to it and she could hear the numerous clicks... . This was without a doubt the last great satisfaction of her life.[6]

The importance of this pioneering step was acknowledged in 1935 when Irène and Frédéric Joliot-Curie were awarded the Nobel Prize.[20] This unique pattern in family relationship from mother to daughter is as directly linear as is conceivable. Yet another intertwining of scientific families occurred when Hélène Joliot-Curie, granddaughter of Marie Curie, married Michel Langevin, grandson of Paul Langevin![7,11]

In 1907, William Duane became the first American to work in her laboratory.[21] He also became one of the few to prepare sealed Ra and Rn sources for insertion into cancerous tissue for treatment. Approximately two years into this project he asked, ''Why waste precious radium on medical work when only radon daughters are used?'' From this idea, he developed the first Ra cow.

Duane returned to Harvard and set up an ''emanation extraction plant''—another Ra cow—for Huntington Memorial Hospital. Many vials of 20 mCi Rn were prepared for radiation therapy and were discarded at half their initial value. These discarded vials of radon were used by Blumgart.

In 1926, Herrmann Blumgart, a distinguished Boston internist, was intrigued by the possibility of injecting radon into human beings to determine the velocity of blood flow in healthy and diseased individuals.[21,22] By crushing the depleted Rn seeds, Blumgart and his associates were able to extract radon and prepare it for injection studies in human beings. These experiments, conducted from 1927 to 1931, served as another set of methodologies and an additional foundation of nuclear medicine. Also, these researches are directly related to the discoveries by Marie Curie.

V. THE BISMUTH STORY

In the last decade of this century is there any identifiable scientific pathway from Marie Curie to the present? Much of her earliest work revolved about bismuth and other naturally decaying elements.[6,23] On June 6, 1898 she had precipitated a new substance from a solution of bismuth nitrate—presumably containing the new element—by adding hydrogen sulfide. Analysis of the precipitate revealed it to be 150 times more active than uranium. Continued precipitations from bismuth revealed increased activity finally leading to the reported identification of polonium. Later that year elimination of bismuth and polonium led to the identification of the more intensively active material that she named ''radium.'' This scenario was the one that led to the current uses of radioactive isotopes of bismuth and related transuranics.

During the remainder of her life, in addition to her many other projects, Marie Curie continued to work in the labora-

TABLE I. Candidate alpha-particle emitters for medical applications.[a]

Source radioisotope (half-life)	Generator radioisotope (half-life)	Administered radioisotope (half-life)
Th-228 (1.91 yr)	Ra-224 (3.66 d)	Bi-212 (60 m)
Th-229 (7340 yr)	Ac-225 (10.0 d)	Bi-213 (45.6 m)
Ac-227 (22 yr)	Th-227 (18.7 d)	Ra-223 (11.4 d)
Th-229 (7340 yr)	Ra-225 (14.89 d)	Ac-225 (10.0 d)
...	Es-225 (40 d)	Fm-225 (20.1 h)
...	Accelerator produced	Al-221 (7.21 h)
...	Accelerator produced	Tb-149 (4.13 h)

[a]See Ref. 25.

tory. Her ongoing interest remained the discovery and characterization of the radioactive elements. Some of these were identified at the time that Marie Curie received her Nobel prizes. Many more were identified in the 1920s and early 1930s by Madame Curie and her associates. At the time of the publication of the 1931 Standards report, nearly all of the elements of the thorium, uranium, and actinium series had been identified and characterized. Included in this group were Bi-212, Bi-214, and Ra-223, which are of current interest today for alpha-emitter radioimmunotherapy.[24,25]

Bi-213 currently appears to be the most useful of these isotopes for such therapy. It was identified only in 1947 by A. English of the National Research Council of Canada[26] as well as the Hageman group at Argonne.[27,28] Elements of the neptunium series, a decay series not found in nature, had been postulated. The isotopes themselves were found following the production of non-naturally occurring isotopes. This was a direct consequence of the discovery of artificial radioactivity by the Joliot-Curies.

The attraction of alpha emitters for biological and medical uses had clearly been recognized for many years especially since the ionization density was a factor of about 10–600 times greater than that of beta and/or gamma emitters. If properly localized in cancer tissue the decay of these atoms provides a very restricted destructive amount of energy, much greater than comparable levels of beta and gamma radiation. The difficulties in using these isotopes are their availability, short half-lives, contamination with beta and gamma rays, and the need for complex chemical separation. Beginning in the late 1980s and continuing to the present, a number of ingenious steps were taken to explore these alpha emitters which are of considerable therapeutic interest. See Table I.[24,25]

These isotopes are then attached to appropriate compounds, such as monoclonal antibodies, chelates, and other biologics.[29,30] The stability, distribution, and turnover of these conjugates is then determined. Phase I clinical trials are currently being conducted using Bi-213 for relapsed acute myelogenous leukemia and with At-211 for cystic gliomas.[25] To date, reactions to these compounds have been minimal in regards to toxicity and systemic acute radiation reactions.

Also of current interest is the possible use of several radionuclides in nuclear medicine which decay by electron capture and/or internal conversion.[31,32] Nuclides emitting these Auger electrons include iodine-123, iodine-125, thallium-201, technetium-99m, etc., which are widely used in diagnostic nuclear medicine.[a)] They can be easily incorporated into ligands capable of being carried to sites of interest. In these nuclides, each decay event results in the emission of several Auger electrons, most of which have very low energies. There is a highly concentrated, localized energy deposition within an extremely small volume, i.e., of the order of a few nanometers.[33] As yet there is limited experience with human beings but animal studies appear promising. Reports detailing characteristics of these nuclides and Auger electrons have been published under the sponsorship of the AAPM by Kereiakes and Rao in a 1992 AAPM report[32] followed by a second report in 1994.[34]

The long-term therapeutic results of the use of these compounds, are not yet known. Although short-term results with alpha emitters are encouraging, follow-up over a period of several years will be required to determine whether therapy with alpha emitters, Auger emitters or combinations of these modalities may result in significant clinical improvement compared to various forms of chemotherapy and radiation therapy currently utilized. Nevertheless this train of events is a direct line from the earliest physics and chemistry of radioactive compounds to the present.

VI. CONCLUSION

Mollie Keller, in her autobiography of Marie Curie, very clearly describes the magnitude of Marie Curie's impact on science[5] She writes:

> The radium that made Marie famous is not her greatest achievement. Her real impact came with that brilliant hypothesis upon which she based all of her life's work: that radioactivity is the result of something happening within the atom itself. Her simple statement spurred other scientists to study the complexity of atomic structure, to seek the solution to the mysterious behavior of the radioelements that Marie exposed in her experiments... . This tiny woman with her decigram of radium turned the world upside down, forever changing the way we look at, understand, and use our environment.

At the time of discovery of artificial radioactivity in 1934, Marie Curie provides the direct link from her work and that of the Joliot-Curies with this elegant statement:

> One could only hope that in the future one could obtain by means of tubes generating accelerated particles radio-elements of which the intensity of the radiation would be comparable to that of natural radio-elements. These new substances could then have medical applications and probably other practical applications.

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[a)]The Auger family was contemporary with the Curies. They summered together at L'Arcouest in Brittany in association with the families of Joliots, Perrin, Debierne, Borel, etc. Victor Auger, Professor of Chemistry, was the father of Pierre Auger, the latter being the discoverer of the Auger effect. The children of this august panoply were playmates and a number of marriages ensued (Ref. 33). Life in this resort is delightfully described in Eve Curie's biography of her mother.

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