

Nuclear Medicine Begins with a Boa Constrictor

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In the beginning, a boa constrictor defecated in London and the subsequent development of nuclear medicine was inevitable. It took a little time, but the 139-yr chain of cause and effect that followed was inexorable (1).

One June week in 1815 an exotic animal exhibition was held on the Strand in London. A young “animal chemist” named William Prout (we would now call him a clinical pathologist) attended this scientific event of the year. While he was viewing a boa constrictor recently captured in South America, the animal defecated and Prout was amazed by what he saw. The physiological incident was commonplace, but he was the only person alive who could recognize the material. Just a year earlier he had isolated the first pure sample of urea—but from the urine of patients with gout!

Upon seeing the unusual feces, Prout sought out the animal caretaker and requested a sample. Grave robbers were an ongoing scandal in London in those days, but coprophilia was a new twist. The incredulous animal caretaker crossed himself

twice and cleaned out the cage. Prout hurried back to his surgery (the British use of the term) with his unusual prize.

In 1815 it was not unusual for a clinical pathologist to practice medicine from his own surgery. It couldn't have been unusual because Prout was the first and only existing clinical pathologist. After getting his MD from the University of Edinburgh, Prout walked the wards of the United Hospitals of St. Thomas's and Guy's until licensed by the Royal College of Physicians on December 22, 1812. In addition to seeing patients, he analyzed urine and blood for other physicians, using methods and laboratory equipment of his own design.

Prout dissolved the snake's feces in muriatic acid and then analyzed the insoluble precipitate. Just as he suspected, it was almost pure (90.16%) uric acid. As a thorough scientist he also determined the “proportional number” of 37.5 for urea. (“Proportional” or “equivalent” weight was the current terminology for what we now call “atomic weight.”) This 37.5 would be used by Friedrich Woehler in his famous 1828 paper on the synthesis of urea. Thus Prout, already the father of clinical pathology, became the grandfather of organic chemistry.

[Prout was also the first man to use iodine (two yr after its discovery in 1814) in the treatment of thyroid goiter. He considered his greatest success the discovery of muriatic acid, inorganic HCl, in human gastric juice. He was first to divide the aliments into three classes: sanguinous (carbohydrate), oliginous (fat) and albuminous (protein). He designed and supervised construction of the Royal Society's first official barometer. From the weather patterns over London he was led by rigid epidemiological reasoning to the cause of London's devastating cholera outbreak; (wrong, of course, but so logical that it puts him in line as grandfather of our modern crusades against cancer).]

In order to determine the proportional weight for urea Prout had to use the “atomic” weights of the involved elements. There were 40–45 chemical elements in 1815 depending upon how many of Davy and Dalton's discoveries you believed. Humphery Davy and John Dalton were sloppy chemists. Thirty-five years later his obituarist would point out that Prout had “a taste for extreme exactitude and unrivaled manual expertness never achieved by John Dalton” (2). Prout remeasured the proportional weights of the elements and noted a remarkable consistency. All of the weights were whole numbers—or very nearly so. He argued that with greater accuracy they would all be multiples of the atomic weight of hydrogen.

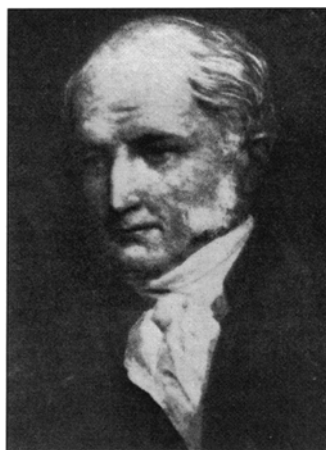


FIGURE 1. William Prout MD, FRS, FRCP (1785–1850).

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Published in an anonymous paper (3) this whole number rule, soon known as Prout's hypothesis, was so highly praised that he quickly acknowledged authorship. But eventually chlorine was its undoing. In 1828 Berzelius proved the atomic weight of chlorine to be midway between 35 and 36. The supposition that half a hydrogen atom entered into the composition of chlorine did violence to Newton's unsplitable atom.

In 1832 the Chemistry Committee of the British Association awarded John Dalton and William Prout 50 pounds to investigate atomic weights and specifically to test the whole number hypothesis. They never did turn in a report because they got involved in an even bigger hassle on chemical nomenclature and formulae. The question of atomic weights was lost in the argument and wasn't "settled" until 1860 when the Belgium chemist, J. S. Stas, measured the weights with great accuracy. He said that the law of Prout was "une pure illusion."

With the Stas measurements, Prout's hypothesis was dead. However, in 1888, William Crookes, a generation more advanced than Stas, arrived at a new conclusion based upon the rapidly developing new technique of spectroscopy. "Probably our atomic weights merely represent a 'mean' value around which the actual atomic weight of the atoms vary within certain narrow limits. . . . when we say the atomic weight of, for instance, calcium is 40, we really express the fact that while the majority of atoms have a weight of 40 . . . a few have 39 or 41, a less number 38 or 42, and so on . . ." (4).

In 1901 Lord Rayleigh voiced a new scientific consensus "the atomic weights tend to approximate to whole numbers far more closely than can reasonably be accounted for by any accidental coincidence" (5). And then in 1913 H. G. Moseley, using crystal defraction, demonstrated that "as we pass from one element to the next using the chemical order of the elements in the periodic system . . . the number of charges is the same as the number of the place occupied by the element in the periodic system" (6). Atomic number, not atomic weight, was critical. The first element, number one at the bottom of the periodic table, was hydrogen. After 98 yr, Prout's hypothesis was no longer a hypothesis. But Berzelius and Stas were not false prophets; they could not possibly have foreseen the relationship until a new observation was made at the very top of the periodic table. And this required an observation on uranium that couldn't be made until spiritualism was revealed in Massachusetts.

THROUGH SPIRITUALISM THE TRUE PATH TO NUCLEAR MEDICINE IS REVEALED

In 1867 Phillip, the youngest brother of William Crookes, died of yellow fever while on a cable-laying expedition in Havana. The circumstances were somewhat confused, and William felt a deep personal tragedy—almost a responsibility. He wanted to know how his brother had contracted this deadly disease (remember, mosquitoes were 30 yr in the future). If he could only talk with his brother. Spiritualism, a recent import from Massachusetts, was all the rage in England at the time, and it offered a means.

Although a religious agnostic, Crookes, along with quite a few of England's top scientists, became intrigued by the "physical phenomena" behind the "psychic force." Table rappings, levitations and apparitions could be investigated by scientific methods. Crookes made some observations and became hooked on the paranormal. He came dangerously close to capturing the Royal Society as an agent for the propagation of spiritualism. But the cult's scientific dishonesty disgusted many scientists. Faraday commented that "many dogs have come to more logical conclusions" (7). But on the surface, Faraday's "fields-of-force" were just as ethereal as Crookes' "psychic-force" and nowhere near as practical—if you wanted to talk to your dead brother. Crookes was almost read out of scientific society. He was deeply hurt by the bitterness of his scientific peers. In his despondency he turned to a piece of scientific scutwork that would saturate his mind.

In 1861 Crookes had discovered the element thallium, but its atomic weight had never been properly measured. If Prout could be called an "exacting chemist" and Stas a "specialist in precision," Crookes became a fanatic. He constructed a new balance enclosed in a specially prepared vacuum case. The expansibility of the weighing arms, knife edges and weighing pans were all measured. The weights were made of a specially purified platinum. The friction of the forceps against the weights during transfer was obviated with especially made platinum hooks. The thallium sample to be weighed and all of the glass and reagents were prepared from multiple purifications.

Crookes used the Tl_2NO_3 method and arrived at an atomic weight of 203.642. The 1961 accepted value is 204.37. If it can be called an error, he made one error. He had used the Stas values for the atomic weights of nitrogen and oxygen. If he had used 1961 values, his atomic weight would have been 204.02.

The important point, historically, is that Crookes knew that he had committed an error—not in his impeccable chemical technique but in the physical concept of "mass." When daylight was shining on his balance the excursions of the balance needle seemed greater than in the dark. There was too much mass in his platinum balance to check this, and so he suspended pith-balls from a straw and balanced these in a vacuum. Different colored rays of light were directed against one ball. It was repulsed by the beam of light, and more by red light than any other color. His demonstration before the Royal Society on April 22, 1874 provoked controversy. Shying away from the controversy, he improved on the unstable pithballs-on-a-straw and on April 22, 1875, demonstrated an instrument he called the "radiometer." Four discs of pith—black on one side, white on the other—were attached to four arms suspended on a steel needle so as to revolve horizontally. The whole was enclosed in a glass globe evacuated to the highest obtainable vacuum. The arms revolved when exposed to visible light. The rate of revolution was proportional to the intensity of the incident radiation. Upon demonstration before the Royal Society the radiometer caused a sensation. To many scientists the first question was, "How did he get that thing into the bottle?"

Maxwell's electromagnetic theory provides for light to exert a pressure. A light particle falling on the black surface would be absorbed and give up its momentum to the vane. Falling on

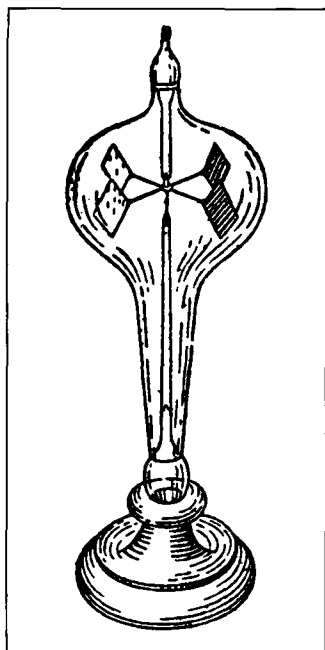


FIGURE 2. Drawing of the Crookes radiometer (c. 1875).

the white surface the light particles would be reflected; the vane would recoil with a momentum equal and opposite to the reflected ray, thus doubling the momentum of an absorbed ray on the black side. Thus, the white side is repelled more than the black side, and Crookes' radiometer will rotate clockwise . . .

But it didn't—it rotated counterclockwise!

Mathematical physicists quivered when they saw the radiometer rotating in the wrong direction. Arthur Schuster (professor of mathematics at Owens College) had another explanation. The few gaseous molecules left in the vacuum globe impinged on both black and white surfaces of the vanes according to the kinetic theory of gases. When light impinges on the black surface it gets hotter, repels the molecules with greater speed, and their recoil rotates the vanes counterclockwise. A colleague suggested that Schuster set up a proof. If the vanes rotated by pressure from light, the globe itself would not be affected. But if the recoil were of molecules inside the globe, it too should rotate but in the opposite direction. At Owens College a radiometer was suspended by a fine thread so that it could rotate as freely as the vanes.

Maxwell's theory was hanging on a fine thread in Owens College. J.J. Thomson described the anxiety of physicists throughout England on the morning of the experiment:

"I can still remember the excitement and anxiety with which I waited for the verdict. And the relief on hearing that the case had rotated in the opposite direction to the vanes" (8).

Crookes had severely shaken but he hadn't cracked the foundations of science.

But making the toy for demonstration was no small task. A laboratory notebook entry by Crookes' lab assistant on March 7, 1876 marks the first rumble of an earthquake that eventually would crumble the foundations:

"Making radiometer for exhibition . . . all went well until putting in bulb when all came to grief . . . had to be taken out,

unsoldered, put in another, when the cup took a piece out of the disk . . . I have tried hard to finish it, but find it impossible today" (9).

Crookes wrote in the notebook under this entry, "Cheer up!" And then he sketched in a tube with platinum anode and cathode embedded into the ends to modify the radiometer. This new tube was the prototype of the "Crookes tubes" that puzzled Roentgen 19 yr later.

J.J. THOMSON CRACKS THE FOUNDATION OF 19TH CENTURY SCIENCE

In Germany a number of physicists had been passing electric currents through evacuated glass tubes that caused the glass to fluoresce. Electricity bore an obscure relationship to light and Crookes thought he could improve upon Johan Hittorf's famous shadow experiment of 1869. In a highly evacuated tube he placed an anode asymmetric so as to leave the path of the cathode ray beam free to strike the glass wall. He also placed a hinged mica maltese cross between the cathode and the glass wall. Upon activation of the cathode a shadow cast by the maltese cross was surrounded by fluorescing glass. After a while the fluorescence began to fade, presumably from fatigue in the glass. A flick of the wrist knocked the cross down and now the shadow itself fluoresced, but the fatigued glass remained dark.

Did this straight-line beam of light (or electricity, in this case) have sufficient mass to rotate his radiometer? He built another modification. In the glass tube he put a pair of glass rails. On the rails a paddlewheel could roll freely from end to end of the evacuated tube. Mica vanes attached to the paddlewheel interrupted the pathway from cathode to anode. He sent a current into the cathode. The paddlewheel rolled toward the anode. He reversed the current. The paddlewheel rolled back. Hence, the cathode rays were particles with mass. J.J. Thomson agreed that they might have mass, but a quick calculation showed that the mass was inadequate to move Crookes' paddlewheel—but he couldn't prove it.

In Germany, Johan Hittorf, a specialist in the transport of ions—atom-sized pieces of matter—should have agreed with Crookes. But he didn't. In 1869 he had put a point cathode into a vacuum bottle, interposed a solid body between it and the glass wall, and produced a sharp shadow in the fluorescence. In 1876 E. Goldstein substituted a very large cathode. It cast a shadow that was not sharp but had an umbra and a penumbra. He introduced the word "Kathodenstrahlen" because these cathode rays cast shadows; hence, like light, they were waves in ether.

This wave-versus-particles controversy lasted until 1895 when Jean Perrin, in France, made another Crookes tube, but this one with a small bucket to collect the ions. He proved that something, and it couldn't be ether waves, accumulated in his collector.

J.J. Thomson, who now agreed with Crookes, modified Perrin's tube and made a long series of measurements to estimate the weights of these "particles of matter." At a Friday evening discourse on April 29, 1897, at the Royal Institution,

he disclosed his results. By indirect measurement the negatively charged particles in the cathode ray beam (he called them "corpuscles," we now call them "electrons") had about 1/1837 the mass of a hydrogen ion. A howl of laughter shook bells as far away as the tower of London. J.J. Thomson was "pulling their legs." It had taken over a century to convince scientists that the atom was the smallest piece of matter. Even Thomson didn't believe his own measurements. He reluctantly conceded error. Upon repetition of the experiment, he found there was error. He had made his corpuscles slightly too large!

Particles of matter smaller than an atom? It was hard to believe, and its significance was not appreciated at the time because every physicist was preoccupied with an even more astounding discovery: the invisible rays of Dr. Roentgen that came out of the Crookes tube.

BECQUEREL BREAKS THE LAW

On Monday, January 20, 1896, the regular meeting of the French Academy of Science featured a demonstration of Roentgen's new photography by Henri Poincaré. The Roentgen story had been leaked to the press 2 wk earlier. (Roentgen didn't give his first paper until January 23, 1896.) But the newspaper article had been well written, and most physicists had a Crookes tube available for a quick check. Poincaré had verified the news story immediately.

Henri Becquerel, as always, attended the meeting. At the end of Poincaré's demonstration, Becquerel asked a question, "From where do these remarkable rays originate?"

"Undoubtedly," answered Poincaré, "from the spot on the glass wall of the discharge tube rendered fluorescent by the impingement of the cathode rays" (10).

Poincaré's answer was technically correct, but Becquerel jumped to the wrong conclusion. Poincaré had not said that fluorescence caused x-rays, but Becquerel's confusion was understandable. His grandfather, Antoine, and his father, Edmund, had been world authorities on light from phosphorescence. As a demonstrator for his father, Henri had prepared a double sulphate of uranium and potassium that was remarkably phosphorescent after exposure to sunlight. If x-rays came from fluorescence on the glass wall of the Crookes tube, obviously they must also come from the intense phosphorescence of the double sulphate of uranium and potassium. Becquerel hurried back to his laboratory to test his misinterpretation.

The story of Becquerel's discovery is well known; the story of the confusion in his mind is not appreciated (11).

The rays from uranium obviously represented the emission of energy. But what was the source of this energy? He proved that it could not come from air surrounding the uranium. It could not come from a chemical reaction. It was a permanent property of all uranium. After hundreds of experiments his interest waned until one of his graduate students, Marie Curie, and her husband Pierre proved that another substance they called polonium gave off, weight for weight, seven hundred times more radiation than uranium. And then, within six months, another substance, radium, was found to give off a million times more radiation than uranium.

By this time, December 1898, Becquerel's break with the conservation of energy law was under severe challenge. He was nibbling away at an explanation for each criticism (including his own disbelief). The Curies gave him a pinhead portion of their first radium sample in a glass vial. He carried the vial in his vest pocket to demonstrate to disbelievers that it gave off light, produced heat, and its radiation did not diminish in time. Soon there were no disbelievers, but there was still no imaginable source for the energy. The law of conservation of energy was dead.

WILLIAM CROOKES OPENS THE 20TH CENTURY IN PHYSICS

When the Curies announced polonium on July 18, 1898, there was considerable criticism: the spectroscope said "Bismuth." The criticism stopped when the master spectroscopist, William Crookes, showed that the only thing wrong with the Curies' discovery was that those French kids didn't know how to do spectroscopy. He made up his own sample of polonium and showed that in between the characteristic bismuth lines were a number of new lines never seen before. Polonium was an element.

Crookes used spectroscopy like we use a pencil. He had been the first to adapt photographic recording and was the recognized world authority on spectrum analysis. But it was only a tool; he was more interested in the impossible dilemma his old friend Becquerel had got himself into: energy coming out of uranium with no possible source for the energy.

In 1900 Crookes prepared a solution of uranium and a ferric salt. He added an excess of ammonium hydroxide and ammonium carbonate. The ferric hydroxide precipitate was intensely radioactive. (Remember, he was using Becquerel's photographic method.) "For the sake of lucidity," Crookes reported, "the new body must have a name. Until it is more tractable I will call it provisionally uranium X—the unknown substance Ex-Uranium" (12). (We now call it ^{234}Th .) He sent off a letter to Becquerel who immediately confirmed the discovery. Crookes had made one slip. He hadn't run a spectrum of the new substance. He *always* did spectroscopy on every material he worked with. He would have fired an assistant who did not verify an analysis with the spectroscope. Uranium X was thorium—Crookes' first spectroscopic discovery 40 yr earlier. Its brilliant green line would have been obvious with only about 15 min additional work. But just this once he forgot, and so he missed the greatest scientific discovery of the 20th century: that the elements were naturally transmuted during radioactive decay. But he made up for this horrible mistake by starting off the process whereby transmutation would be discovered.

If he could wash some radioactivity out of uranium, maybe Becquerel was wrong. Maybe all of the radioactivity could be washed out. He made some crystals of uranyl nitrate, did multiple ether separations, evaporated the ether for multiple fractional distillations. After many repetitions he was satisfied and tested his "pure" uranium on a photographic plate—the exposure was a total blank. He put the mother solution on a photographic plate, all the radioactivity was in the solution.

With straightforward chemistry Becquerel's "always active" uranium had been washed clean of radioactivity. He immediately wrote to Becquerel, "I've washed the radioactivity out of your uranium," and told him how to do it.

Upon opening the envelope, Becquerel exploded, "Impossible," and immediately repeated the experiment. He confirmed Crookes . . . but not quite. By this time Becquerel was using the electroscope in addition to the photographic method; the precipitate was very weak but not totally inactive. The mother solution, as Crookes had written, contained almost all the activity.

Becquerel was puzzled. What could he have done wrong to make such a mistake four years earlier when he proved that all uranium was "always" radioactive? A few months later he was still worried. He wasn't one to make that kind of mistake. So he dug out the 4-month old samples and measured them again. On this repeat measurement the uranium was again hot, but now the mother solution was cold. He dashed off a note to Crookes, "Measure your samples again!" Then he began all over from scratch. Crookes broke his daily routine to check Becquerel. His 4-month old cold uranium sample was now hot. The hot mother solution was now cold. After making some new uranium crystals, he too began all over from scratch.

When Crookes received the note from Becquerel, he had been writing to Rutherford telling him where to buy pure thorium nitrate. After checking Becquerel's finding, he added a paragraph describing the disappearance of radioactivity in UX and its regrowth in the parent uranium. Upon receiving Crookes' letter, Rutherford immediately checked all of his old thorium X samples: washout and regrowth were also true for thorium X.

But what was this thorium X? No such thing had ever been announced as a radioactive element.

THE THIRD SACRED COW OF 19TH CENTURY SCIENCE IS KILLED

It would be historically interesting to read the first draft of the Rutherford-Soddy paper on the radioactivity of thorium compounds. The published second draft gives the first hint of "transmutation" (13). But how, in the first draft, could they have explained the concentrations of short-lived (55 sec) radioactivity growing out from the extremely long-lived (^{14}Gy) thorium? Rutherford admits that it can't be explained, and in the middle of a paragraph ThX suddenly creeps in as the explanation. (ThX is a 3.6-day isotope of radium.) Rutherford contradicts himself in mid-paper and proves that thorium X is different from thorium. While writing the paper, undoubtedly stretching his imagination for an explanation, Crookes' uranium X had been announced. Rutherford immediately did the same type of experiment with thorium and discovered thorium X, but he never announced it. The new element just crept into the corrected draft of the paper he was already writing.

Upon receiving this note from Crookes on the regrowth of uranium and the decay of uranium X, he immediately checked his old thorium X samples. All of his cold thorium precipitates

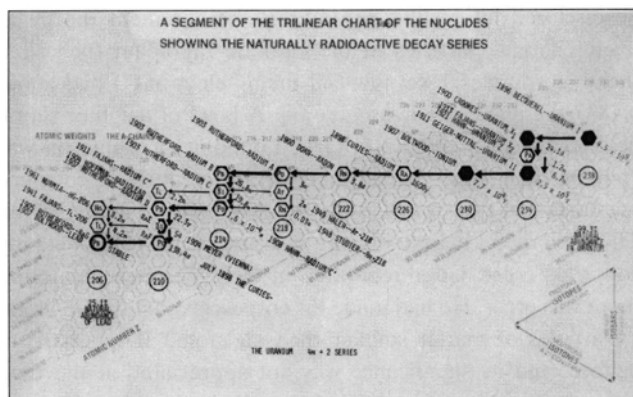


FIGURE 3. Uranium natural decay series.

were hot again and all the hot thorium X samples were now cold.

[Forget that you know of the existence of isotopes and then look at today's chart of nuclides (Fig. 3). You will then understand the impossible position that Rutherford was in. Uranium decays to thorium, which decays back to uranium, which decays back to thorium. Then look at thorium (Fig. 4). It decays to radium, which decays back to thorium, which decays back to radium. A more perfect system of concealment (without isotopes) is hard to imagine.]

Rutherford had originally said, "There can be no question ThX and [Crookes'] UX are distinct types of matter with definite chemical properties." The thorium manuscript was in press before Christmas (14). Upon opening Crookes' letter, Rutherford was astonished to see confirmation of his article which hadn't even been printed yet, and by no less than Crookes and Becquerel. He immediately wrote another article (15). This time he included the forbidden words he had been thinking, "the radioactive elements must be undergoing spontaneous transformation."

In 1897 J.J. Thomson's electron showed there were pieces of matter smaller than the atom, which was hard to swallow. By 1899 radium proved that Becquerel had broken the law of conservation of energy; it had to be believed, whether or not it was hard to swallow—you could see the radium glow. In 1902 Rutherford's "transmutation" was not a public sensation, it

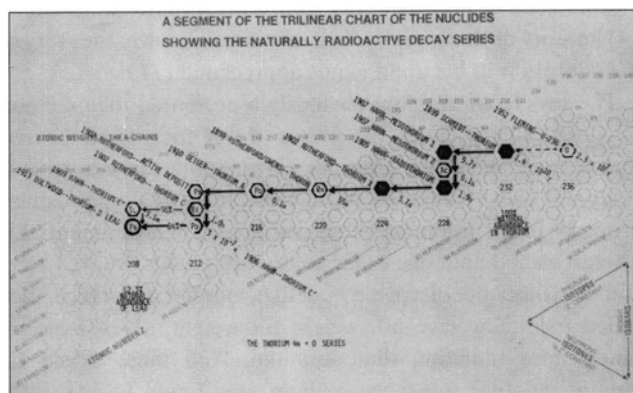


FIGURE 4. Thorium natural decay.

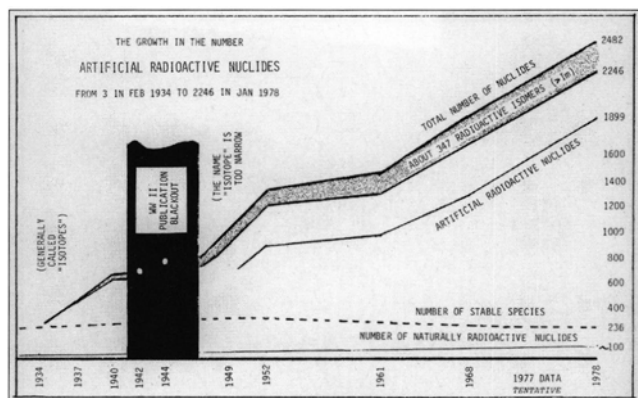


FIGURE 5. Number of nuclides, 1934–1978.

was a scientific obscenity—not mentioned in polite conversation. His senior colleagues at McGill begged Rutherford not to publish the second thorium article because it would bring disgrace upon McGill (16).

IRENE CURIE COMPENSATES FOR DELAYING THE DISCOVERY OF POLONIUM

Marie Curie was awfully pregnant in 1897. Two embryos were developing. One was the idea of getting her doctor's degree. Mathematics? Physics? Chemistry? Equally proficient in all three, she inclined towards chemistry, and the subject would be an extension of Becquerel's interesting new uranium rays. After nine months delay waiting for Irene to be born, plus another nine months gestation, in July 1898 polonium was discovered. Although overshadowed by the radium discovery six months later, polonium had a higher energy alpha emission than radium, and it decayed to a clean stability. Irene, the first embryo, felt a kinship to polonium and used it (not the same chunk, but a very similar piece) to bombard aluminum foil 36 yr later.

It was already known in 1933 that some light elements when exposed to alpha particles would emit neutrons and positrons. Irene and her husband Frederick Joliot were working on the possibility that high-energy gamma rays could produce positron-electron pairs. A thin metal foil was exposed to a polonium source until a burst of radiation was detected. This radiation, of course, ceased immediately upon removal of the polonium and the experiment was over. One morning the Joliot-Curies noticed that the experiment was not over:

Our latest experiments have shown a very striking fact; when an aluminum foil is irradiated the emission of positrons does not cease immediately. . . . The foil remains radioactive and the emission of radiation decays exponentially as for an ordinary [naturally occurring] radioelement. We observed the same phenomenon with boron and magnesium. . . . the transmutation of boron, magnesium, and aluminum by alpha particles has given birth to new radioelements emitting positrons (17).

The new radiation must be, they thought, from an isotope of phosphorous. Irene's long gestation in chemistry with Marie

now paid off; she quickly dissolved the aluminum foil in HCl and separated out a pure phosphate which continued to give off radiation with a half-life of 2.5 min. This chemical conversion proved that a new, artificially radioactive isotope had been produced. Joliot suggested adding the prefix "radio-" to distinguish these unstable from stable isotopes.

Upon reading the Joliot and Curie note in *Nature*, Enrico Fermi in the Royal University at Rome saw an easier way to produce these new species without the severe limitations of the alpha source. He obtained some radon (630 mCi) from a medical radium cow and sealed it with beryllium in a glass vial to produce neutrons. He put the vial in a can of paraffin to slow down the neutrons. With this enormous (at least it was the biggest so far), slow neutron source, Fermi irradiated every pure element he could find (eventually 60 in all). Three months later in a letter to the editor of *Nature* (18), he reported 14 radio-elements. The 11th item was interesting: "Iodine—Intense Effect. Period about 30 Minutes." (Robley Evans in Boston read this note and 2 ½ yr later remembered those seven words.)

Although the Joliot-Curies discovered isotopes, they were not the first to produce them. For over a year the cyclotron at Berkeley had been producing them in great quantities. F.N.E. Kurie told the story at the dedication of the new U.S. Navy Radiation Laboratory at San Francisco in 1955:

Ernest Lawrence invited Dr. Cooksey and me to come out to Berkeley in the summer of 1932 and see if we couldn't repeat the Cockroft-Walton transmutations. We came out with boxes of Geiger counters which at that time were not very common. The ones Cooksey and I brought out were designed for a particular job, and when it was done they were thrown away. An all-purpose Geiger counter was not known in most laboratories with the result that even though we were simply crawling with artificial radioactivity, we were not the first to discover it.

We learned about radioactivity one morning in 1934 when a cable came from the Curie-Joliot's telling us about their experiment. We verified it. This should have been a lesson, but several months later we got a cable from Fermi telling us that he had discovered that neutrons could make things radioactive. These great discoveries, which really set nuclear physics on the way, were followed by a period of relative stability in which we all found that an easier way to make a living was simply to bombard something new and find new radioactivity. A paper could always be written, and papers were the things that counted. So, literally, for years people would take things and bombard them; then they'd take the neighboring elements of the periodic table and try to figure out what the activities really were.¹

From 3 radioisotopes in February to 14 three months later—and the number was growing; by the end of 1934 at least 40 radioisotopes had been reported. Upon receipt of Fermi's

¹Kurie's words, but not a direct quote: I have shortened the story considerably. (From the U.S. Navy Program of the Dedication.)

cable, the Berkeley group—a rare combination of chemists and physicists—focused a new look at the constitution of matter. The periodic table with stable isotopes was almost complete. (A few numbers, 43 (Tc), 61 (Pm), 85 (At), and 87 (Fr) were still missing.) But now the table was growing again. In his review of the changing table (of December 2, 1936), the University of Chicago chemist, Aristid Grosse (who had envisaged the possibility of artificial radioactive isotopes in 1932), pointed out that “it may be now safe to assume that the little over 400 isotopes [263 stable and 141 radioactive] represent the largest bulk of possible atomic species” (19). Grosse was grossly wrong; by 1942 Robley Evans listed 656 isotopes, by 1944 Glenn Seaborg listed 746 and updated his list to 1,314 in 1952.

SULLIVAN CHARTS THE SPECIES

During the last days of 1912 Kasimir Fajans had announced that more than one of the naturally occurring radioactive nuclear species could occupy the same place on the periodic table. By the end of 1913, Frederick Soddy had generalized this to all elements and had adopted the term “isotope.” By this time F.W. Aston had diffused neon through clay pipe to prove that the two lines J.J. Thomson had detected in his 1912 parabolic spectroscopy of neon were not a contamination; the two lines were separate and distinct components. This was the first proof of the existence of isotopes for physicists.

At the spring 1914 meeting of the Bunsen-Gesellschaft in Leipzig, Max Lambert, who Fajans had sent to work with T.W. Richards at Harvard, reported on the different atomic weights of lead from different mineral sources. Chemists were now convinced of the existence of isotopes and the officers of the Bunsen-Gesellschaft gave a special toast to Fajans—he had explained the difference without violating the periodic system.

By 1917 more stable isotopes had been found, and Soddy pointed out that if there were isotopes with “the same atomic number but different atomic weight” there must also be species with “the same atomic weight but different atomic number.” The British chemist, A.W. Stewart, in 1918 called such species “isobares” (the final “e” was later dropped and the A-chains became “isobars”).

When the neutron was discovered a decade later the definition of “isotope” was changed from atomic weights and numbers to the structural relationship of protons and neutrons. Isotopes were nuclear species with an equal number of protons (their chemical identity is implied). Isobars were nuclear species with an equal number of protons-plus-neutrons (identity of atomic mass is implied). In 1934 the German physicist K. Guggenheimer pointed out that there must be a third set—nuclear species with an equal number of neutrons. Replacing the “p” (for protons) with an “n” (for neutrons), the name “isotones” was coined.

All of these words are plural. The single species in series can be part of either an isotopic or an isobaric or an isotonic chain. In 1939 the Dutch physicist, J. Belinfante, proposed the term “nuclon” (changed to “nucleon” by C. Møller in 1941). It, however, became associated with specific “mass number,” and the word “nuclide” was slowly substituted.

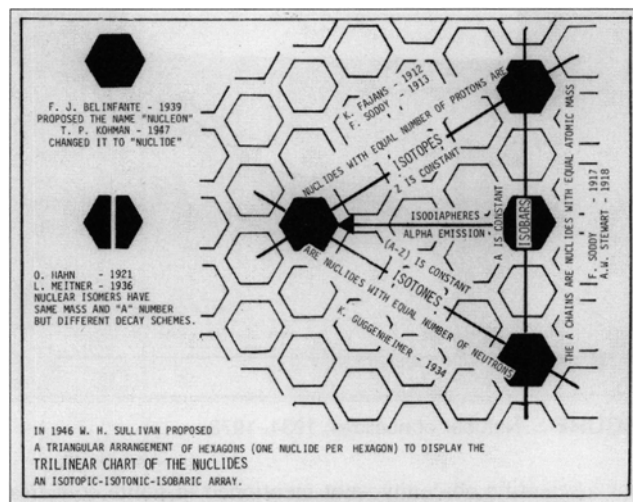


FIGURE 6. Nomenclature of nuclides. It took a half century to coin the word “nuclide” to signify a specific nuclear species of atom in a chemically elementary form of matter.

Way back in 1921 Otto Hahn had found that uranium Z (Pa-234) had the same atomic number and the same atomic weight as uranium X₂ (Pa-234), but had a different half-life. By 1935 quite a few of these freak isobaric-isotopic-isotones were detected. Lisa Meitner in 1936 saw an analogy with chemical isomers and called them “nuclear isomers.”

During World War II at the Manhattan District’s Clinton Laboratories (about to become AEC’s Oak Ridge National Laboratory), a great number of unreported nuclides were being worked with. Analytic chemists on the project were finding so many possible reactions in one irradiation that identification required immediate access to long tables that did not give a picture of what might have occurred. Most nuclides decayed by isobaric transition towards stability; the isobars had to be visualized as related. Since chemical identification was required, the isotopes had to be listed in sequence. In Oak Ridge, where neutron bombardment was the prime method, a sequence of nuclides by neutron number was also required.

William H. Sullivan, a chemist at Clinton Labs, tried to organize the rapidly changing nuclear data into an immediately visible form. Since the three important axes, neutron number—proton number—and atomic mass number, were equally important he tried trilinear coordinate paper. A hexagon has three axes and so he placed each nucleon in a hexagon (Fig. 6). When placed on a beehive array, a chart of the elements in nuclear structure was formed. His first chart in four colors (20) was 16 ft long unfolded. It contained 935 hexagons, each with up to 13 items of nuclear data. It was out of date before the chart was printed.

For the second edition (21), the words “nuclear species” had already been replaced by the more popular “nuclides.” The new chart was 17 ft long unfolded, but it did not go out of date because gummed hexagonal stamps were issued periodically to keep the data up to date. By 1961, after nine issues of gummed stamps had been distributed, the chart contained 1349 hexagons with many double or even triple isomers. But the data by now was becoming so complex that a Nuclear Data Group (first at National Academy of Science—NRC, then at Oak

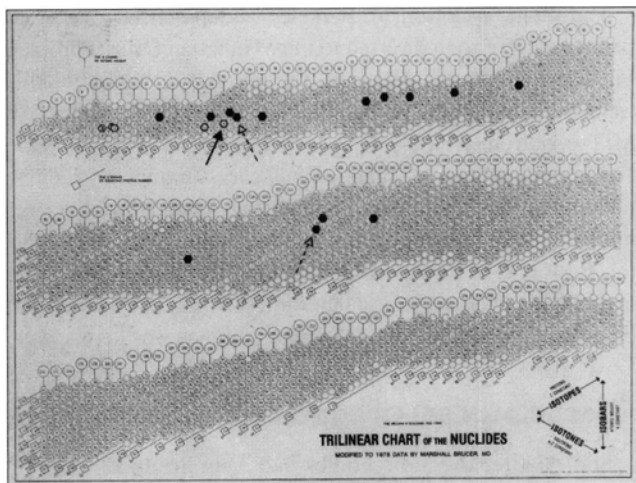


FIGURE 7. The first radioactive nuclides: February 10, 1934. Joliot F. Curie I (Paris): radionitrogen, radiosilicon and radiophosphorus produced by the action of α -particles. *Nature* 133:201, Feb. 10, 1934. March 14, 1934. Crane HB, Lauritsen CC (Cal Tech); "Induced Radioactivity" in C-11 and N-13 by proton bombardment. *Phys Rev* 45:497, April 1, 1934. April 10, 1934. Fermi E (Rome): Fourteen "Unstable Products" of neutron bombardment. *Nature* 133:757, May 19, 1934.

Ridge) had to go back to the tabular form, and thick volumes of Nuclear Data Sheets are still being revised and published periodically (22). After Sullivan's death a further simplification of the chart, showing only half-life and decay data, was published by Mallinckrodt. Its revision in 1979 will have 2250 hexagons, including 250 for stable nuclides and 59 for nuclides with $t_{1/2}$ over a million years. I haven't counted the isomers yet. The rapid expansion seems to have slowed down. (I am not as certain of this as Grosse was in 1937.)

ROBLEY EVANS MAKES IT MEDICAL

Even before the concept of isotopes had been announced George de Hevesy, then with Rutherford in Manchester, had used naturally occurring radioactive lead as a "tag" to study the dispersion of radioactivity in stable lead. This tag concept required that the chemistry of two disparate nuclear species be identical. In 1927 Hermann Blumgart used a dilute solution of radon as a "tracer" during the first few seconds after injection into the blood stream. The "tracer" required that there be no physiologic recognition of the foreign nuclide. A "tag" could be a "tracer" but the "tracer" need not necessarily be a "tag." By the time artificial radionuclides were discovered both concepts had already found a use in biological and medical research but not in the practice of medicine.

On November 12, 1936, Karl Compton, president of the Massachusetts Institute of Technology (MIT), was scheduled to address a luncheon in Vanderbilt Hall at Harvard Medical School. His subject: "What Physics Can Do For Biology and Medicine." Robley Evans, on his physics faculty, had slipped him some juicy, physico-biologic tidbits about Hevesy's indicator-dilution studies in animals using radioactive tags. Attending the lecture was James H. Means, whose thyroid clinic at



FIGURE 8. Robley Evans, Ph.D. Nuclear "medicine" begins on Nov. 12, 1936. In Vanderbilt Hall at Harvard Medical School. J.H. Means, M.D. (Thyroid Clinic, Mass. Gen. Hosp.): "Is there a radioisotope of iodine?" Robley Evans, Ph.D. (Physics, Mass. Inst. Tech.): "We can make some."

Massachusetts General Hospital (MGH) was already world-famous, accompanied by two of his henchmen, Earle Chapman and Saul Hertz. Hevesy's ^{32}P work was considered very interesting, with possible clinical application, but, asked Means in the post-lecture discussion, "Is there a radioactive isotope of iodine?" (23) At this point Robley Evans remembered the seven words he had read in Fermi's article 2 $\frac{1}{2}$ yr earlier. He explained that there was a radioiodine, and it could be made the same way Hevesy made ^{32}P .

During the next six months Compton and Means set up a joint MIT-MGH committee to study the feasibility of Evans' interesting idea. Evans knew that MIT could not afford the fantastically expensive 600-mg radium-beryllium neutron source that Hevesy had used. But he knew how Fermi had made his neutron source with medical radon. Huntington Hospital in Boston used many radon needles milked from their radium cow, and discarded them after a short decay. For no cost at all he could gather the discards, mix their remnant activity into beryllium and make a baby brother to Hevesy's neutron source. He put his gadget together, and within a few months proudly showed Compton a few nanocuries of ^{128}I . The thyroid project was feasible; Compton and Means raised \$3,000 to start a joint MGH-MIT thyroid-radioiodine research program. Evans persuaded a versatile physicist, Arthur Roberts, to join the full time staff and concentrate on radioiodine production. In late 1937 he and Saul Hertz injected some ^{128}I into the ear of a rabbit.

After hours of neutron bombardment they hadn't made enough ^{128}I for more than a teaser. Fortunately a retired physician donated his collection of radium plaques and needles; this new permanent 110-mg Ra-Be neutron howitzer could produce an enormous yield of about $1/20 \mu\text{Ci}$ of ^{128}I every day. Now they could really study thyroid metabolism. Hertz, Roberts and Evans published the first paper on thyroid-radioiodine in May 1938 (24).

Meanwhile, they had encouraged Joe Hamilton, a young neurologist working in Berkeley's Medical Group, to also study ^{128}I metabolism in animals. He was giving enormous (a new definition of enormous) doses produced by the cyclotron. Anything Berkeley could do, MIT could do better. Compton and

Evans went to the Markle Foundation in New York for \$30,000 to build a cyclotron.

Joe Hamilton was dissatisfied with the limitations imposed by the 25-min half-life of ^{128}I in studying metabolism. One day in the spring of 1938, he ran into Glenn Seaborg on the steps of LeConte Hall at Berkeley. Hamilton complained bitterly about the ^{128}I short half-life, "Why can't you make me an iodine isotope with a longer half-life?" "How long a half-life do you want?" asked Seaborg. "Oh, about a week."

Seaborg and his physicist partner, Jack Livingood, prepared some tellurium targets and a week later Seaborg delivered the first and only radioisotope ever discovered to fill a physician's prescription. This sample was of a new 8-day ^{131}I (25).

Hamilton, a nonpracticing physician, saw the clinical implications of the MIT-MGH collaboration. He joined forces with Mayo Soley, an internist from across the bay, and by October 1939, Hamilton, Soley and Eichorn published the first paper on the diagnostic use of ^{131}I in patients (26). (This was not our " ^{131}I ," it was a mixture of at least 10 isotopes of iodine.) By July 1940, autoradiograms showed the actual distribution of ^{131}I in normal, thyrotoxic and nontoxic goiters, and its absence in nonfunctioning, malignant thyroid tissue (27).

Four months later the MIT cyclotron produced its first sample of ^{130}I , a 12-hr half-life nuclide; its radiopurity seemed ideal for therapy. By January of 1941 the first patient was given a therapeutic dose of ^{130}I by Hertz at MIT, and a 30-patient program was started.

But radioiodine was not the first "isotope" to be used therapeutically. After much work with ^{32}P in animals and then tracer studies in patients, John Lawrence gave the first therapeutic dose of a "radioisotope" to a patient with chronic lymphatic leukemia on Christmas Eve, 1937. The treatment seemed to be quite successful. One of his students, Lowell Erf, was definitely successful in treating polycythemia vera with ^{32}P during the next few years. In December 1939, ^{89}Sr was used as a convenient radioactive substitute for calcium (because calcium nuclides were not available). Excellent uptakes in metastases to bone were observed by Charles Pecher at Donner Lab. Within a year ^{89}Sr became the second radioisotope to be used in therapy. If diagnostic and animal physiology studies were included in a survey of radioisotope work prior to 1941, there is a hint of practically everything that would later become a part of nuclear medicine. But, on hindsight, one diagnostic study is of overriding importance.

The group at Columbia Physicians and Surgeons in New York came up against a pertinent question. Did a metastasis from thyroid carcinoma store radioiodine? Judging from some of their tissue sections, it looked possible. So they gave a patient with metastatic thyroid carcinoma a dose of radioiodine. One of their radiology residents, Robert Ball, was given a GM tube and told to find the metastases by counting the clicks. He was slowly scanning the patient's entire body (it was manual and without automatic recording, but nevertheless scanning). The work was rather boring, so he turned on the radio to ease the tedium. Suddenly the music stopped and a voice announced, "Pearl Harbor has been bombed!"

The 60-in. cyclotron at Berkeley and practically all of the personnel were soon diverted to the Manhattan District problem. Physicians in Boston, and in all the hospitals using radioiodine, were given higher priority duties. During the wartime secrecy, the MIT cyclotron, which had been dedicated to and maintained 100% medical priority, supplied millicurie amounts of radioisotopes to 36 hospitals. These 36 hospitals (plus a few that were muzzled by the atom bomb project—Berkeley, Chicago, Rochester, Boston, Oak Ridge, Columbia) represented the entire effort in medical radioisotope research for a five-year period. Scholarly priorities cannot be ascribed because so much was kept secret.

SAM SEIDLIN SELLS CONGRESS A CANCER CURE

Shortly after the atom bombs had been dropped (August 6 and 9, 1945), Colonel K.D. Nichols of the Manhattan Project suggested that, in view of the "virtually unlimited production" of isotopes, they should be authorized for distribution to outsiders. In January 1946, Paul C. Aebersold, a physicist who had been with the Berkeley group before the war, was asked to transfer from Los Alamos to take charge of isotopes distribution from Oak Ridge. During the first months of 1946 this new isotopes branch had no methods or preparation, packaging, shipment, routes, advertising or billing procedures. With no precedents to follow, Aebersold invented the only bureaucratic procedure that has ever worked before or since. He wrote memoranda for his superiors in Oak Ridge to send to their superiors in Washington. The next day he flew to Washington to be on hand when the memoranda were delivered. That same day he prepared directives for the superiors in Washington to send to his superiors in Oak Ridge. That same day he flew back to Oak Ridge to receive his own directions from his superiors' superiors on the now official procedure. This method has never been improved upon in the history of bureaucracy.

On June 14, 1946, six scientists and 30 newspapermen were invited to Oak Ridge to see the "isotope facilities." (Thus, a science/publicity ratio was established for the next 30 yr.) An announcement was made in *Science* that radioactive isotopes were available to qualified investigators (28). After months of battle in Congress over military versus civilian control, the Atomic Energy Act of 1946 released isotopes from military control. The very next day, August 2, 1946, Pennsylvania newspapers announced the first shipment of radioisotopes to the University of Pennsylvania Hospital. But if you read the Chicago papers the real first shipment was made to the University of Chicago; and if you read the Minneapolis newspapers the real first shipment was made to the University of Minnesota; and if you read the San Francisco newspapers the real first shipment was made to the University of California. Thirty or forty orders for radioisotopes had been shipped immediately.

There was no first shipment. At a carefully staged ceremony in front of the Oak Ridge reactor, 200 mCi of ^{14}C were handed to Dr. E.V. Cowdry of Barnard Free Cancer Hospital of St. Louis. Radioisotope propaganda had been centered on the cure of cancer. The "first shipment" had been carefully selected because of the "Free Cancer Hospital" name (and, incidentally, Martin Kamen, then in St. Louis, had discovered

^{14}C back in 1941). Kamen converted the “first shipment” to a tagged acetic acid which went to Antioch College in Ohio where Dr. P. Rothmund used it to prepare a cancer-producing (not a cancer-curing) agent. The bulk of the “first shipment” was used by Dr. Simpson at Barnard Hospital for study of the production of skin cancer in mice.

Fortunately for nuclear medicine a true cancer cure had occurred. In 1943 Samuel Seidlin, an endocrinologist in New York City, had been called in to treat a patient suffering from hyperthyroidism even though the thyroid had been removed years before for thyroid carcinoma. The hyperactive metastases were successfully destroyed with radioiodine, and this was a true cure by any definition. On December 7, 1946, the fifth anniversary of the bombing of Pearl Harbor and in the midst of congressional indecision on atomic controls, the *JAMA* published the single most important article in the history of nuclear medicine (29).

Seidlin had published a preliminary article, but it was from the *JAMA* article that newspapers picked it up, and a remarkable transposition occurred into newspaperese, “Cancer Cure Found in the Firey Canyons of Death at Oak Ridge.” Within days, every congressman heard from his constituency. Within hours, the brand new AEC commissioners knew they now had two jobs: to stockpile bombs behind closed doors, and to pour money into cancer research out in the open. During the next 10 yr, nuclear medicine was nurtured on the strength of the Seidlin article.

PAUL AEBERSOLD AND DONALEE TABERN SELL ISOTOPES

Radioisotopes suddenly became available with a built-in promoter. Paul Aebersold's isotopes division was the only safely nonsecret part of AEC. Aebersold had unlimited funds, unlimited radioisotopes and, seemingly, unlimited energy to promote the unlimited cures that had been held back from the American public for too long. The liberal establishment was in the depths of shame for having ended the war by killing people. Radioisotopes didn't kill people; they cured cancer.

Aebersold spoke at every meeting of one person or more that had one minute or more available on its program. No matter what the meeting's subject, Aebersold's topic was always the same. He sold isotopes. Aebersold had to keep an account of the progress being made with radioisotopes for the new Joint Committee on Atomic Energy in Congress. He tried to maintain a complete record of all published articles in which radioisotopes were used. (This “complete” bibliography was published by AEC in his 3-, 5- and 8-year summaries.) By 1955 the U.S. atomic monopoly was broken, but by this time even Aebersold's office staff could not keep up with the deluge of articles.

During the first five years, 3200 articles were published on the use of radioisotopes. There were 375 on the physical properties of new radionuclides and most were on some form of chemistry. But 949 papers had some relationship to medicine. Forty-three had virtually the same title—some variety of “Gee Whiz, Look at What We've Done.”

The AEC did not sell drugs; they sold a radionuclide with a disclaimer on its use as a drug. A number of commercial

suppliers got into the distribution business, but it was probably Abbott Laboratories who were first to sell a pharmaceutical grade of the AEC product. Then in 1948 one of their chemists, Donalee Tabern, stumbled on the first true radiopharmaceutical (in Hymer Friedell's Group at Western Reserve in Cleveland). J.P. Storaasli had measured the blood volume of 30 patients using radioiodinated human serum albumin. Abbott trademarked a pharmaceutical grade of this as “RISA.”

While the rest of us in early nuclear medicine were engulfed in details, precision, legislation and preparing papers for publication, Aebersold toured the country extolling the virtues of radioisotopes. Tabern, however, did not give speeches. He met personally with any physician who gave the slightest hint of interest. He sold them on the value of nuclear medicine (and incidentally on the Abbott product). Then he told them which instrument to buy, taught them how to use it and then filled out their license application to AEC. He addressed the letter, furnished the stamp and mailed it to AEC.

In a very practical sense, nuclear medicine couldn't have advanced very far without a radiopharmaceutical industry. The industry could not have existed without AEC promotion. With 30 yr of hindsight, I think Aebersold and Tabern were pioneers as much as were the Fathers of Nuclear Medicine—at least they were our Dutch Uncles.

A SOCIETY TO DISPENSE KNOWLEDGE IS FORMED

The deluge of papers, speakers and especially publicity was not without its response from vested interests in organized medicine. A large group of radiologists highly resented ^{60}Co teletherapy, which could never take the place of 250-Kv x-ray. The annexation of thyroid therapy by an unorganized group of internists, pathologists, radiologists (and even by a physicist or two) was resented by many surgeons who felt they dominated the field. Many internists deplored the attempts at treatment of malignant effusions with ^{198}Au colloid by an unorganized array of radiologists, pathologists and surgeons (and even a chemist or two). Some clinical pathologists were driven up the wall by the motley group of internists, surgeons and radiologists (and even a technician or two) who showed disrespect for the time-tried and scientifically tested BMR. As the scintillation counter with its complex scale-of-64 electronics gained favor, physicists sneered at medics dabbling in equipment they couldn't possibly understand. An outstanding biochemist at Vanderbilt pointed out that the answer to leukemia lay in the use of semi-log graph paper and that medics counted on their fingers (he, incidentally, moved his lips when reading medical reports).

A few men in the Pacific Northwest who used “isotopes” in a small part of their regular work recognized that no one person could be competent in physics, chemistry, engineering, electronics, radiobiology, mathematics and at least ten clinical specialties. Jeff Holter set up a Montana Society of Nuclear Medicine in 1953 so they could talk about their mistakes. (Holter, a physicist, was responsible for dumping the name “radioisotopes” as the first mistake to be corrected.) The Montana organization never met formally because a few friends from Seattle, Portland, and Vancouver, B.C. wanted to join.

On January 19, 1954 twelve men met in the Davenport Hotel in Spokane, Washington (the compromise central point of the region). Within minutes Jeff Holter became the first officer (pre-first election) of the society, "we had a voluntary assessment of ten dollars to pay for rooms, booze and food, and I was treasurer with an even \$100.00." (Twelve men at \$10 each? To this day, Jeff has not accounted for the extra \$20.)

Asa Seeds was elected secretary—and on February 17, 1954, the first newsletter of the society of Nuclear Medicine was sent to practically everybody he could think of. I'll quote directly from the newsletter:

The Spokane meeting was attended by Doctors R.L. Huff (Research Physician, Seattle), R.G. Moffat (Internist, Vancouver, BC), E.T. Feldsted (Radiologist, Vancouver, BC), C.P. Wilson (Internist, Portland), A.K. Atkinson (Radiologist, Great Falls), T.T. Hutchens (Internist, Portland), A.C. Seeds (Radiologist, Vancouver, WA), M. Harris (Internist, Spokane), N.J. Holter (Physicist, Helena), W.H. Hanna (Med. Physics, Bremerton, WA), J.P. Nealen (Physicist, Spokane), and T. Carlile (Radiologist, Seattle). These 12 individuals agreed that there was sufficient reason to organize a society, and ultimately the name "The Society of Nuclear Medicine" was adopted. It was decided that there would be no geographical designation in the name as it might have wider appeal than the Northwest. . . . Officers were elected and it was decided that the first annual meeting should be May 29th and 30th in Seattle. . . . the president, in his enthusiasm, has written a number of letters, including one to Paul Aebersold which resulted in a tentative acceptance for the speaking engagement. . . . some of you will also be interested to know that Don Tabern of Abbott Laboratories, in response to a letter from me, immediately sent a check for \$10.00 and announced his intentions to come to the meeting on May 29th and 30th. [Thus, after the founding group, Tabern became the first dues-paying member of the society.]

The first annual meeting was opened at the Benjamin Franklin Hotel in Seattle, Washington, on Saturday morning May 29, 1954, by President Thomas Carlile. It was attended by 109 physicians, physicists, chemists and technicians. The first paper presented was by Rex Huff on "Estimates of Cardiac Output by In Vivo Counting of ^{131}I -Labeled HSA." Ten papers followed through Saturday and Sunday morning. On Sunday noon at the closing session, Jeff Holter declared the meeting to be the finest ever held in the history of the Society of Nuclear Medicine.

It had taken 139 years to make such a society possible. Six generations of physicists and chemists participated in the growth of the idea.

Although the cream of London's scientific society attended that wild animal exhibition on the Strand in London in 1815, only William Prout, a practicing physician trained in scientific measurement to observe sick people, had the experience necessary to be astounded by the feces of a boa constrictor.

POSTSCRIPT

The logo of the Southeastern Chapter of the Society of Nuclear Medicine shows a snake entwined around a stick with some rays in the background. Most people think it symbolizes the staff of Aesculapius over a diagram of the atom. It doesn't. It is a boa constrictor in Valsalva maneuver in the rising sun.

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