THE EARLY HISTORY OF THE USE
OF RADIOIODINE IN THYROID DISEASE

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Since much of my career in medicine and thyroidology has, in a way, been in some kind of equilibrium with radioactive isotopes, and radioiodine in particular. I thought it would be interesting and fun to look into the details of how radioiodine was first used for the study of the thyroid. Familiar names and interesting people were involved and original sources were still available to probe for information. In essence it is a tale of the two cities of Cambridge and Berkeley involving the introduction of a new technology in two quite different settings (slide). I would like to thank so many who have taken the time to help me learn about how it all happened. Robley Evans, Patricia Durbin, Vitta Hertz and Earle Chapman have been particularly generous in sharing their recollections and their files.

The story began on November 12, 1936 at a regular Thursday Colloquium in the large dining room in Vanderbilt Hall at Harvard Medical School. Karl Compton, then president of MIT, lectured a group of the Harvard faculty on the subject of "What Physics Can Do For Biology And Medicine."

For Compton's speech, Robley Evans, one of his faculty, had proposed the mention of radioactive indicators and their potential for studying metabolic mechanisms. The suggestion of an isotopic tracer intrigued the members of the MGH Thyroid Clinic attending - including J. Howard Means, Earle Chapman, Saul Hertz, and Jacob Lerman, and precipitated a question about the possible avail-
ability of a radioactive isotope of iodine. Compton didn't know but said he would look into it.

Things were happening rapidly in the world of physics at that time. In February 1934, (slide) the Joliot-Curies had described the discovery of artificial radioactivity. Within 3 months, in May 1934, Enrico Fermi (slide) at the Royal University at Rome using a slow neutron source irradiated every pure element that he could find and reported making 14 radioactive elements. The next slide enlarges part of his paper and shows that the 11th isotope listed was "iodine-intense effect, period (i.e. half-life) about 30 minutes." When Compton looked for an answer to the query about iodine isotopes, Evans recalled that brief statement in Fermi's paper. On December 15th, (slide) Compton wrote to Hertz telling him that an iodine isotope – I^{128} with a half-life of 25 minutes – could be made relatively easily.

During the subsequent 6 months, Compton and Means set about developing a joint project on the production and use of radioactive iodine. Robley Evans was then working with Joe Aub on the radium dial painters (slide - shows Evans in 1936 measuring the radioactivity content of a radium (Ra^{226}) poisoning patient with a primitive whole body counter). Evans set about to develop a method of making radioactive iodine. He needed a source of neutrons and for this he gathered as many used radon needles and reprocessed radium placques as he could from the Huntington
Hospital and prepared a radon-beryllium neutron source that could be used to irradiate ethyl iodide.

The next slide shows this fairly primitive device (fortunately Dr. Evans is not only an inveterate photographer but also apparently has never thrown anything out and has kindly sent me his original photographs). The radon-beryllium mixture was embedded in a small barrel of paraffin to slow the neutrons. Containers of ethyl iodide were irradiated for an hour or two and the $^{128}$ produced was extracted with a water solution containing a few mg of free iodine and sodium bisulfite. Evans assigned Arthur Roberts, a young MIT physicist to this project. Means asked Saul Hertz to represent the Thyroid Clinic.

The next slide shows Hertz, on the left with Roberts on the right, injecting $^{128}$ into a rabbit's ear in studies starting in May 1937.

The maximum initial radioactivity available from Evans's neutron source corresponded to about 1/20th of a uCi of $^{128}$! This miniscule amount of radiiodine was injected into each of 48 rabbits and its tissue distribution followed. Early investigators had to make their own Geiger-Müller detector tubes and this proved a significant task in view of the sensitivity needed for the very small amounts of fast disappearing radioactivity. With a 26 minute half-life,
They had 40 minutes working time during which there was measurable activity. The next slide shows Roberts using his homemade counter and a vacuum tube amplifier measuring the activity in a rabbit tissue sample. Tissue samples were minced and spread on a flat surface which was placed in direct contact with the counter.

Their first paper was published in May 1938 (slide). In it they described the rapid early uptake of iodine over 30 minutes (slide - the normal animal - lowest curve - was compared to animals with hyperplastic glands from thyrotropic hormone injections - (top curve with triangles), and from animals receiving an exclusively cabbage diet (next curve with x). In this first paper Hertz, Roberts and Evans (slide) suggested the potential diagnostic and therapeutic use of radioisotopes of iodine.

It was clear that stronger sources and longer lived isotopes were necessary for expanded studies. The Van de Graaf electrostatic generator was then being developed at MIT but it seemed preferable that they get their own isotope generator and for this, Evans preferred a cyclotron. At this time, only one other radioisotope of iodine was known, 12 hour I^{130} although the 13 day I^{126} had just been discovered.

With the interinstitutional collaboration seemingly established and the preliminary rabbit work with I^{128} proving so successful,
Compton and Evans visited the John & Mary Markle Foundation offices in New York on the morning of May 19th, 1938 to request support. By great good fortune, Walter B. Cannon, a consultant to the Foundation just happened to be there. When the data and the idea of a medical cyclotron was presented, Cannon was particularly taken with the potential of the project and strongly recommended approval. The Markle Board had a short executive session with Cannon and then told Compton and Evans to write the proposal. To give you an idea of the simple life of the 1930’s, Evans tells me that they went back to the Hotel Commodore, found the hotel stenographer and had her type a short letter that they brought back to the Markle office that afternoon. They received their $30,000 grant to construct a cyclotron then and there, and as Dr. Evans puts it, they caught the good old New Haven railroads’ Merchants Limited for dinner and the train-ride back to Boston.

Cyclotron construction at MIT began in the Fall of 1938 (slide) and by November 1st, 1940 went into full operation as the world’s first cyclotron built exclusively for biological and medical use. Its first product was the 12.5 hour I\(^{130}\) obtained from deuteron bombardment of tellurium targets but it contained a contaminant of about 10% of I-131.

Until the MIT cyclotron went on-line, targets were sent to Berkeley where Evans had been a graduate student with Ernest Lawrence and to Rochester for cyclotron irradiation. These targets,
Once irradiated, were mailed back to Boston by first class mail. Roberts and Evans' second paper, now with means added as a co-author, was presented at the 1939 meeting of the American Association for the Study of Goiter and published first in the Transactions of the Society. They reported that the normal thyroid collected up to 80 times the quantity of iodine expected from diffusion but that the hyperplastic thyroid collected up to several hundred times that expected. Non-radioactive iodine (KI) was noted to lower radioiodine accumulation. They found these effects to be specific for iodine since radioactive bromine did not collect in the thyroid. Evans even calculated that to deliver 100 roentgens to a 75 gram human thyroid would require about 750 mCi, an impossibly large amount of radioactivity for that time.

This study was also the first in which potential of multiple iodine isotopes as tracers was realized. Although most studies were done with 25 minute I\textsuperscript{128}, 12.5 hour I-130, 8 day I-131 and even more 13 day I-126 were also used. The long half-life iodine isotopes were obtained from Ernest Lawrence and his assistant Joe Hamilton at the Berkeley cyclotron laboratories.

This is probably a good time to move our story to Berkeley and to Joe Hamilton, a young physiologist who received his M.D. in 1936 from the University of California in San Francisco. He was not interested in clinical medicine and went to the Radiation
Laboratories at Berkeley first as a graduate student and then in 1937 as a Research Fellow although maintaining an appointment in Neurology at the medical school across the Bay.

Lawrence and his associates had discovered the cyclotron in 1932 and had been producing isotopes since that time. To their chagrin, they had initially not recognized that their products were radioactive until they received a cable from the Joliot-Curies in 1934 telling them about their work inducing artificial radioactivity. Subsequently, Lawrence's team set their up Geiger counters and bombarded almost anything they could get their hands on - it was that easy to make radioisotopes! By the end of 1934, at least 40 radioisotopes had been reported and with additional cyclotrons joining the fun, the number went to 400 by 1936 and 656 by 1942.

Hamilton began his studies at Berkeley in 1936 by measuring the route and speed of absorption of several radioactive elements including iodide. (Slide - about 1937 shows Hamilton (on the left) and Alfred Marshall (on the right) drinking radioactive sodium - with his right hand on a Geiger counter).

In his first paper, submitted August 18, 1938, Hamilton acknowledged the assistance of Mayo Soley for suggestions and criticism. He then turned to Soley as his primary collaborator for his thyroid studies. Soley was a 1933 Harvard graduate and
an Intern and Resident at the MGH. In 1935 he went to the University of California and by 1939 was an Assistant Professor of Medicine and Pharmacology and in charge of their thyroid clinic.

Hamilton was unhappy, as was Hertz, with the constraints of the 26 minute half-life of $^{128}$I but surprisingly, appeared unaware that a 13 day half-life $^{126}$I had been announced 7 months earlier in February by Tape & Cork at Michigan. Incidentally, Tape & Cork also described an 8 day half-life isotope which they thought was tellurium-131 but which turned out to be iodine-131. It was easy to make radioisotopes but often difficult to be sure what they were.

Glenn Seaborg, later to receive the Nobel Prize for his discovery of many radioisotopes was then a radiochemist at Berkeley who prepared the radioisotopes from the cyclotron targets. He recalls that Hamilton met him on the steps of the physics building at Berkeley in the Spring of 1938 complaining about the short half-life of $^{128}$I for biological studies. Seaborg says that he asked Hamilton how long a half-life he wanted and Hamilton said "how about a week?" Seaborg reports that he went back to the cyclotron and with his partner, Jack Livingston, prepared some tellurium targets which they bombarded in the 37 inch cyclotron with 8 MeV deuterons and neutrons. Within a week they found an 8 day iodine isotope, $^{131}$I. They didn't waste much time reporting it (slide) their announcement appeared in the June 15th, 1938
issue of Physical Review. Incidentally, Seaborg's mother later developed hyperthyroidism and he was particularly pleased to tell her that the $^{131}\text{I}$ she received for treatment was his discovery.

Although the longer 8 day half-life solved the problem of working time other problems remained because bombardment of tellurium produced a mixture of iodine isotopes which Hamilton had to "age" to obtain "predominantly" $^{131}\text{I}$. Pure $^{131}\text{I}$ would not be available for another seven years when it could be separated from fission products.

Hamilton and Soley turned their attention (now late in 1938) to studying iodine metabolism using the new 8 day $^{131}\text{I}$. Probably inspired by Hertz' initial paper published about 6 months earlier, they set about measuring thyroid uptakes (slide) as well as rates of excretion of $^{131}\text{I}$ in patients making use of the energetic $\gamma$-ray of this isotope. For adequate counts, the detector which was relatively insensitive to $\gamma$ rays had to be placed in direct contact with the neck. Incidentally in their publication they acknowledged the support of the New Deal Works Progress Administration.

They also studied a number of patients who received radioiodine before thyroidectomy and prepared some beautiful radioautographs of the thyroids (slide). These are copies of Hamilton's original slides given to me by Patricia Durbin, a colleague of Hamilton. (The histologic section is on your left and the autoradiograph on the right). They show, in his words, "little $^{131}\text{I}$ accumulation in the distended acini but show that the cells and
smaller acini have a greater ability to store isotope." The next slide showing no uptake in a thyroid cancer (upper right) was typical of the results of all investigators to that time.

Hamilton and Soley’s paper published in 1939 was remarkably sophisticated and made good use of the long half-life of $^{131}$I (slide). Thyroid uptake measurements (ordinate) were obtained for as long as 5 days (abscissa) along with assays of urine and stool radioactivity. They suggested that studying rates of uptake and discharge by the thyroid would "give a dynamic picture of iodine metabolism in normal and goiterous glands" and would be helpful in diagnosis. They also examined the problem of carrier (non-radioactive) iodine (slide) and showed that the then standard 14 mg of carrier KI given with the tracer (right) was sufficient to markedly depress uptake, particularly in hyperthyroid patients, as compared to the elevated uptake seen on the left.

The next slide shows Hamilton (on the left) a little later—probably 1940—when he was the director of the Crocker Cyclotron Laboratory with Martin Kamen (who discovered Carbon-14 a year later), and what fortuitously appears to be the formula for a Bromine substituted iodothyronine.

During the war Hamilton worked for the Manhattan Project at Berkeley on the biology and metabolism of plutonium and fission products. The next slide shows Hamilton in April 1955 shortly before his death from leukemia (in February, 1957) — attributed in his obituary to industrial overexposure to radiation.
To return now to Boston, it appears that the first therapeutic use of any radioiodine was by Hertz and Roberts with $^{130}\text{I}$ in January, 1941. By early May, 1942 they were able to present the results of treatment of 10 patients at the meeting of the American Society for Clinical Investigation in Atlantic City. This slide shows a page from the proceedings of the meeting and here is the paper by Hertz and Roberts. Hertz at that time was ill with colitis and Roberts presented the paper and Means telegraphed Hertz (slide) that it went well. However, Roberts says that there were no questions after the presentation and I have talked to a number of people who were at the meeting and who do not recall that anybody seemed particularly impressed with the presentation.

Let me call your attention (slide) to another paper on the same program, this by Hamilton and Lawrence on "Recent Clinical Developments in the Therapeutic Application of Radiophosphorus and Radioiodine." In this paper they reported the first use of P32 for polycythemia vera. They also reported the oral administration of $^{131}\text{I}$ to three patients with hyperthyroidism (this was the first human treatment with $^{131}\text{I}$ and was given on October 12, 1941. However, the first hyperthyroid patient treated with any iodine isotope was by Hertz 9 months earlier. John Lawrence gave me this next slide which Hamilton used in his presentation and which shows the effect of the radioiodine on the
BASAL METABOLIC RATE OF THE THREE PATIENTS.

These results are particularly interesting because of the small amounts of radioiodine used - under 1 mCi of I-131 - but with most impressive responses - with improvement within 4 to 6 weeks and complete remission in 2 of the 3 patients by four months. This result is difficult to understand since today 5 to 10 times this amount of I$^{131}$ is required for effective treatment. The most likely explanation lies in the problem of radioisotope assay which plagued the early workers. It was not unusual to find the millicurie differing by a factor of 2 to 5 in different laboratories. It is also likely that the early I$^{131}$ included other iodine isotopes some of which (such as I-125) had not yet been discovered and which could not be detected by the means then available.

The next stage in this saga occurred when Hertz entered the Navy in April 1943 and asked Earle Chapman to take over his radioiodine treated patients. Chapman (slide - about 1941) soon discovered that many of Hertz's patients were taking potassium iodide making clinical evaluation difficult and some were still hyperthyroid. Most of these patients had received KI - shortly after the radioiodine - apparently at Means' insistence. This became a point of contention and controversy. Means commented somewhat defensively in a paper in 1949 (slide) that he felt it necessary to follow radioactive iodine with "ordinary iodine"

".....to protect the patients against the mischief from thyroiditis during a period in which treatment of unknown efficacy
was being tried out."

Early in 1946, Morris Fishbein (slide) then editor of the JAMA wrote to Means about two manuscripts he had received on the treatment of hyperthyroidism with radioiodine. They both came from the MGH Thyroid Clinic, both used the same \( ^{130}I - ^{131}I \) mixture from MIT, and both thanked Means for his support - but both had different authors! Fishbein - diplomatically-asked Means for clarification. Means - also diplomatically - wrote back explaining simply that they were two different excellent series. Fishbein took the hint and so in the May 11, 1946 issue of the JAMA (slide - this is a paste-up) there were two papers on radioiodine treatment of hyperthyroidism from MGH. The first, on page 81, was a follow-up of 29 patients treated by Hertz and Roberts in 1941 and 1942....and the second on page 86 was a new series of 22 patients treated by Chapman and Evans.

Both of these papers were presented a month later in Chicago on June 20 at the annual meeting of this organization. Hertz's paper received honorable mention for the Van Meter prize. The printed discussion emphasized Hertz' concern that Chapman's radioiodine doses, 14 to 78 mCi, were "inordinately large," as compared to the 1 to 28 mCi that Hertz had used. At the same time, Hertz found it necessary to defend his use of ordinary iodine - KI which Chapman reported had confounded the clinical evaluation of the patients.
The issue of the appropriate dose of I-130 was never resolved because one week earlier Science of June 14th, 1946 (next slide) announced that fission produced radionuclides in large quantities and high purity were immediately available from the Manhattan Project.

That announcement opened the modern radioisotope era. In the following year (1946), 407 shipments of radioactive materials for medical therapy were made and by five years later the number had risen tenfold — most of which was I\(^{131}\).

To complete my story I must shift back to 1941 where in New York a young biochemist named Albert Keston, working at Columbia with Virginia Frantz obtained I-130 from MIT and gave it to a patient with thyroid cancer. They reported in 1942 finding 6% uptake in the thyroid but 30% in a metastasis in the right femur. Most of the previous studies in thyroid cancer were in individuals with intact thyroids. It was only later that they learned that this patient had a prior partial thyroidectomy. This information was the clue that led to the effective therapeutic strategy for the management of thyroid cancer.

About this time, Sam Seidlin at Montefiore Hospital in New York had a quite remarkable patient with hyperthyroidism due to metastases from thyroid cancer. Seidlin negotiated with Evans for radiiodine and bought one hour’s worth of cyclotron time for
ABOUT $1800 (WHICH USED UP HIS ENTIRE ANNUAL RESEARCH BUDGET) AND FOR THIS ONLY GOT 102 mCi \textit{^{130}I}. HOWEVER, THE UPTAKE IN THE METASTASES WAS VERY HIGH AND THE TUMORS RECEIVED A SUBSTANTIAL RADIATION DOSE. TO MAXIMIZE THE EFFECT FROM THE EXPENSIVE ISOTOPE, EMIL J. BAUMANN WHO RAN THE CHEMISTRY LABORATORY AT MONTEFIORE HOSPITAL AND WHO HAD COLLABORATED WITH DAVID MARINE ON MANY THYROID STUDIES, EXTRACTED THE RADIOIODINE FROM THE URINE (SLIDE) SO IT COULD BE READMINISTERED TO THE PATIENT. A YOUNG VOLUNTEER WAS ASSIGNED THE TASK OF PURIFYING THE URINE. HER NAME WAS ROSLYN SUSSMAN AND SHE HAD RECENTLY MARRIED AARON YALOW A PHYSICIST ON THEIR TEAM. SHE TELLS ME THAT THIS WAS HER FIRST CLINICAL EXPOSURE TO RADIOIODINE.

THE EFFECTS OF THIS RADIOIODINE TREATMENT WERE SO IMPRESSIVE THAT THE PATIENT'S CANCER WAS CONSIDERED CURED AND WHEN THIS REPORT WAS PUBLISHED IN DECEMBER, 1946, IT HAD A MAJOR PUBLIC IMPACT. NEWSPAPER HEADLINES FEATURED WHAT WAS CALLED A REMARKABLE NEW CURE FROM AN ASTOUNDING AGENT FROM THE FIERY CANYONS OF DEATH AT OAK RIDGE AND NOW AVAILABLE AS A RESULT OF THE WAR EFFORT. THIS SENSATIONAL STORY HELPED MOBILIZE PUBLIC AND CONGRESSIONAL SUPPORT TO CONVINCE THE AEC COMMISSIONERS OF THE IMPORTANCE OF FACILITATING OAK RIDGE ISOTOPE DISTRIBUTION FOR MEDICAL USE.

THESE NEW ISO TOPE TECHNIQUES SPREAD RAPIDLY FROM THE TWO INITIATING GROUPS ALTHOUGH IN SOMEWHAT DIFFERENT WAYS. IN BOSTON, THE THYROID CLINIC SENT MANY GRADUATES FANNING OUT OVER THE COUNTRY
and others came to learn what was going on. Sam Haines of the Mayo Clinic sent a young research fellow, Ray Keating, to spend 6 months at MGH in 1942 to learn radioiodine techniques. Others such as Rulon Rawson later came from the MGH to New York to work on thyroid cancer and Robert Williams then at the Thorndike went to Seattle. Brown Dobyns, Bengt Skanse, John Stanbury, and many others learned how to use radioisotopes at the Thyroid Clinic.

From Berkeley, diffusion of information followed a slightly different path in that Mayo Soley continued the thyroid work after Hamilton was diverted during the war to plutonium biology. Soley was joined by Earl Miller and later Glenn Sheline both radiologists who continued and expanded the studies of radioiodine treatment. The clinical use of radioiodine on the West Coast was primarily in the hands of radiologists although there were notable exceptions such as Paul Starr who had worked at the MGH Thyroid Clinic in the late 1920's. I suspect that the early West Coast radiologists interest and experience eventually led to the development of the specialty of Nuclear Medicine as we know it now.

From the point of view of both thyroid physiology and clinical practice, radioiodine arrived at just the right time. By 1938, work on iodine metabolism had all but stopped due to the limitations of the existing chemical techniques although Salters' and Sam Barker's work on blood iodine was about to produce the
DIFFICULT BUT RELATIVELY ACCURATE PROTEIN-BOUND IODINE DETERMINATION.

As for therapy, by 1940, the mortality of surgical thyroidectomy had been reduced to a minimum of 2% in the hands of experienced surgeons, although 7 to 10% was far more usual. In June 1942, Astwood was to treat his first hyperthyroid patient with thiourea and open an entirely new era of therapy. By the early 1950's the increasing use of radiiodine for the treatment of hyperthyroidism was so prevalent that Lindon Seed lamented is his 1968 presidential address to this organization that this period saw the demise of the goiter surgeon.

The history of radiiodine from Compton's colloquium to the announcement in Science was a brief 10 years but it included many remarkable coincidences and chance events. It also has many elements of personal tragedy with the deaths of both Saul Hertz and Mayo Soley by suicide and of Joe Hamilton from overexposure to radiation.

The developments in Berkeley and Cambridge support the thesis of the sociologists of science that identical discoveries occur simultaneously in different locations. They might also have some comments to make about the diffusion of technology in different settings and its impact on
the increasing dehumanization of medicine. One could even make significant deductions about the effects of federal regulation on scientific progress or of financial constraints upon the introduction of new technologies.

Instead, I would like to emphasize that this short history which encompassed many problems and conflicts is the history of a discovery with significant impact - a success story. Interdisciplinary cooperation and collaboration succeeded, and there was rapid and effective spread of information and technical knowledge - particularly by personal contacts through a network of investigators who cared about what they were doing and about the patients whose care was entrusted to them.

It is this kind of network that contributes to productive science, and it is this kind of network of people with common interests and goals that is the essence of the American Thyroid Association. Our organization is a fellowship for communication, collaboration, teaching, and sharing. This fellowship is the reason our forbears came together 60 years ago, why we are here tonight, and why the Association will continue.

Twenty or thirty years from now the story of radioiodine will be vastly different - with one exception - the beginnings will have remained the same. The past is of interest and offers its lessons but it is the future to which we must now look and learn and contribute.
Sam Barker
William Blahtd
Earle Chapman
Patricia Durbin
Rabley D. Evans
Sam Haines
Vitta Hertz
Sidney Ingbar
John Lawrence
Jacob Lerman
Farahe Maloof
William McConahey
Earl Miller
William Myers
E. Eric Pochin
Rulon Rawson
Arthur Roberts
Glenn Seaborg
Glenn Sheline
Lester VanMiddelworth
Sidney Werner
Roslyn Yalow
Artificial Production of a New Kind of Radio-Element

By F. Joliot and I. Curie, Institut du Radium, Paris

SOME months ago we discovered that certain light elements emit positrons under the action of \( \alpha \)-particles\(^1\). Our latest experiments have shown a very striking fact: when an aluminium foil is irradiated on a polonium preparation, the emission of positrons does not cease immediately, when the active preparation is removed. The foil remains radioactive and the emission of radiation decays exponentially as for an ordinary radio-element. We observed the same phenomenon with boron and magnesium\(^2\). The half life period of the activity is 14 min. for boron, 2 min. 30 sec. for magnesium, 3 min. 15 sec. for aluminium.

We have observed no similar effect with hydrogen, lithium, beryllium, carbon, nitrogen, oxygen, fluorine, sodium, silicon, or phosphorus. Perhaps in some cases the life period is too short for easy observation.

The transmutation of beryllium, magnesium, and aluminium \( \alpha \)-particles has given birth to new radio-elements emitting positrons. These radio-elements may be regarded as a known nucleus formed in a particular state of excitation; but it is much more probable that they are unknown isotopes which are always unstable.

For example, we propose for boron the following nuclear reaction:

\[
\text{B}^{11} + \text{He}^{4} = \text{N}^{13} + \alpha^{4}
\]

\( \text{N}^{13} \) being the radioactive nucleus that disintegrates with emission of positrons, giving a stable nucleus \( \text{C}^{14} \). In the case of aluminium and magnesium, the radioactive nuclei would be \( \text{Si}^{17} \) and \( \text{P}^{17} \) respectively.

The positrons of aluminium seem to form a continuous spectrum similar to the \( \beta \)-ray spectrum. The maximum energy is about \( 3 \times 10^4 \) e.v. As in the case of the continuous spectrum of \( \beta \)-rays, it will be perhaps necessary to admit the simultaneous emission of a neutrino (or of an antineutrino of Louis de Broglie) in order to satisfy the principle of the conservation of energy and of the conservation of the spin in the transmutation.

The transmutations that give birth to the new radio-elements are produced in the proportion of \( 10^{-1} \) or \( 10^{-4} \) of the number of \( \alpha \)-particles, as for other transmutations. With a strong polonium preparation of 100 millimicrons, one gets only about 100,000 atoms of the radioactive elements. Yet it is possible to determine their chemical properties, detecting their radiation with a counter or an ionisation chamber. Of course, the chemical reactions must be completed in a few minutes, before the activity has disappeared.

We have irradiated the compound boron nitride (BN). By heating boron nitride with caustic soda, gaseous ammonia is produced. The activity separates from the boron and is carried away with the ammonia. This agrees very well with the hypothesis that the radioactive nucleus is in this case an isotope of nitrogen.

When irradiated aluminium is dissolved in hydrochloric acid, the activity is carried away with the hydrogen in the gaseous state, and can be collected in a tube. The chemical reaction must be the formation of phosphine (PH\(_3\)) or silicon hydride (SiH\(_3\)). The precipitation of the activity with zirconium phosphate in acid solution seems to indicate that the radio-element is an isotope of phosphorus.

These experiments give the first chemical proof of artificial transmutation, and also the proof of the capture of the \( \alpha \)-particle in these reactions\(^1\).

We propose for the new radio-elements formed by transmutation of boron, magnesium and aluminium, the names radionitrogen, radiosilicon, radiophosphorus.

These elements and similar ones may possibly be formed in different nuclear reactions with other bombarding particles: protons, deuterons, neutrons. For example, \( \text{N}^{13} \) could perhaps be formed by the capture of a deuteron in \( \text{C}^{11} \), followed by the emission of a neutron.

\(^1\) Ired Curie and F. Joliot, J. Phys. et Rad., 4, 494; 1933.

\(^2\) Ired Curie and F. Joliot, C.R., 193; 1934.

\(^3\) Ired Curie et F. Joliot, C.R., meeting of Feb. 29, 1934.
Letters to the Editor

[The Editor does not hold himself responsible for opinions expressed by his correspondents. Neither can he undertake to return, nor to correspond with the writers of rejected manuscripts intended for this or any other part of Nature. No notice is taken of anonymous communications.]

Radioactivity Induced by Neutron Bombardment

Experiments have been carried out to ascertain whether neutron bombardment can produce an induced radioactivity, giving rise to unstable products which disintegrate with emission of β-particles. Preliminary results have been communicated in a letter to La Ricerca Scientifica, 5, 282; 1934.

The source of neutrons is a sealed glass tube containing radium emanation and beryllium powder. The amount of radium emanation available varied in the different experiments from 30 to 630 millicuries. We are much indebted to Prof. G. C. Trabacchi, Laboratorio Fisico della Sanità Pubblica, for putting at our disposal such strong sources.

The elements, or in some cases compounds containing them, were used in the form of small cylinders. After irradiation with the source for a period which varied from a few minutes to several hours, they were put around a Geiger counter with walls of thin aluminium foil (about 0.2 mm. thickness) and the number of impulses per minute was registered.

So far, we have obtained an effect with the following elements:

- Phosphorus—Strong effect. Half-period about 3 hours. The disintegration electrons could be photographed in the Wilson chamber. Chemical separation of the active product showed that the unstable element formed under the bombardment is probably silicon.

- Iron—Period about 2 hours. As the result of chemical separation of the active product, this is probably manganese.

- Silicon—Very strong effect. Period about 3 minutes. Electrons photographed in the Wilson chamber.

- Aluminium—Strong effect. Period about 12 minutes. Electrons photographed in the Wilson chamber.

- Chlorine—Gives an effect with a period much longer than that of any element investigated at present.

- Vanadium—Period about 5 minutes.

- Copper—Effect rather small. Period about 6 minutes.

- Arsenic—Period about two days.

- Silver—Strong effect. Period about 2 minutes.

- Tellurium. Period about 1 hour.

- Iodine—Intense effect. Period about 30 minutes.

- Chromium—Intense effect. Period about 6 minutes. Electrons photographed in the Wilson chamber.

- Barium—Small effect. Period about 2 minutes.

- Fluorine—Period about 10 seconds.

The following elements have also given indication of an effect: sodium, magnesium, titanium, zirconium, zinc, strontium, antimony, selenium and bromine. Some elements give indication of having two or more periods, which may be partly due to several isotopic constituents and partly to successive radioactive transformations. The experiments are being continued in order to verify these results and to extend the research to other elements.

The nuclear reaction which causes these phenomena may be different in different cases. The chemical separation effected in the cases of iron and phosphorus seems to indicate that, at least in these two cases, the neutron is absorbed and a proton emitted. The unstable product, by the emission of a β-particle, returns to the original element.

The chemical separations have been carried out by Dr. O. D’Agostino. Dr. E. Arnaud and Dr. E. Segrè have collaborated in the physical research.

Enrico Fermi.

Physical Institute,
Royal University, Rome.
April 10.
Letters to the Editor

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- **Phosphorus**—Strong effect. Half-period about 3 hours. The disintegration electrons could be photographed in the Wilson chamber. Chemical separation of the active product showed that the unstable element formed under the bombardment is probably silicon.

- **Iron**—Period about 2 hours. As the result of chemical separation of the active product, this is probably manganese.

- **Silicon**—Very strong effect. Period about 3 minutes. Electrons photographed in the Wilson chamber.

- **Aluminum**—Strong effect. Period about 12 minutes. Electrons photographed in the Wilson chamber.

- **Chlorine**—Gives an effect with a period much longer than that of any element investigated at present.

- **Vanadium**—Period about 3 minutes.

- **Copper**—Effect rather small. Period about 6 minutes.

- **Arsenic**—Period about 2 days.

- **Oxid**—Strong effect. Period about 2 minutes.

- **Tellurium**—Period about 1 hour.

- **Indium**—Intense effect. Period about 30 minutes.

- **Chromium**—Intense effect. Period about 6 minutes.

Electrons photographed in the Wilson chamber.

- **Barium**—Small effect. Period about 2 minutes.

- **Fluorine**—Period about 10 seconds.

The following elements have also given indication of an effect: sodium, magnesium, titanium, zirconium, zinc, strontium, autunomy, selenium and bromine. Some elements give indication of having two or more periods, which may be partly due to several isotopic constituents and partly to successive radioactive transformations. The experiments are being continued in order to verify these results and to extend the research to other elements.

The nuclear reaction which causes these phenomena may be different in different cases. The chemical separation effected in the cases of iron and phosphorus seems to indicate that, at least in these two cases, the neutron is absorbed and a proton emitted. The unstable product, by the emission of a beta-particle, returns to the original element.

The chemical separations have been carried out by Dr. O. D’Agostino, Dr. E. Amaldi and Dr. E. Segré have collaborated in the physical research.

**Enrico Fermi**

Physical Institute,
Royal University, Rome.
April 10.
December 15, 1936

Dr. S. Hertz
Massachusetts General Hospital
Boston, Mass.

Dear Dr. Hertz:

To my chagrin I have just come across the memorandum which I made on your question about the radioactivity of iodine.

Iodine can be made artificially radioactive. It has a half period of decay of twenty-five minutes and emits gamma rays and beta rays (electrons) with a maximum energy of 2.1 million volts. It is probable that there are several other periods of decay, but if so they correspond to types of radioactivity like the one indicated and they are not as yet very definitely established.

Very sincerely yours

KTC/L

President
Radioactive Iodine as an Indicator in the Study of Thyroid Physiology.  

S. Hertz, A. Roberts and Robley D. Evans. (Introduced by Henry Jackson.)

From the Thyroid Clinic, Massachusetts General Hospital, Boston, and the Physics Department, Massachusetts Institute of Technology, Cambridge.

The known facts of thyroid physiology indicate that iodine is selectively taken up by the thyroid gland, and that in some measure that gland's function is regulated by its iodine content. Artificial radioactivity may be induced in a variety of elements by means of neutron bombardment. It seemed that the possibility of using "tagged" (radioactive) iodine as a physiologic indicator was one which demanded investigation.

Ethyl iodide (600-1000 cc) was irradiated in a paraffin-surrounded bottle by immersing it in a neutron source consisting of 110 mg of radium mixed with beryllium in a sealed tube. The radioactive iodine thus obtained was concentrated by a method which has been described elsewhere. The precipitate of radioactive silver iodide, which was dissolved in a solution of 0.5-1.0 g of sodium thiosulphate, and then diluted to 10-15 cc for intravenous injection. In a series of 48 rabbits, no toxic effects from the acute administration of such quantities were experienced. Aliquot portions of the solution of radioactive iodine used for injection were withheld for measurement of radioactivity.

*This work was aided by a grant from the Milton Fund of Harvard University.

1 Roberts and Irvine, Phys. Rev., 1938, 58, 609.
Comparison of the quantities of iodine collected by normal rabbit thyroid glands in the same time (15 minutes) when the amount injected is varied. They further tend to show that under conditions of thyroid stimulation (hyperplasia), the collection in the same time is increased severalfold. It is therefore logical to suppose that when strongly active materials are available the concentrating power of the hyperplastic and neoplastic thyroid for radioactive iodine may be of clinical or therapeutic significance.

Recently the discovery of a new radioactive isotope of iodine has been announced. This isotope has a half-period of 13 days. It is obvious that it will have many advantages over the 26-minute isotope for both indicator and therapeutic work. Such experiments as the above may now be extended over much longer time intervals following injection.

We are indebted to Professor J. H. Means of the Harvard Medical School for his stimulating interest in this work.

*Tape and Cork, Phys. Rev., 1938, 58, 676 A.*
LETTERS TO THE EDITOR

Radioactive Iodine Isotopes

We have bombarded tellurium with 8 Mev deuterons and have found two new radioactive iodine isotopes, with half-lives of 13 hours and 8 days. The latter is created by two mechanisms: (1) by the decay of radio-tellurium and (2) by direct transmutation from stable tellurium. Process (1) is demonstrated by the fact that successive extractions of iodine, from the same solution of bombarded tellurium, show a growth of the 8-day period; this must therefore be associated with either $I^{138}$ or $I^{138}$, as the second activity of a double decay: $Te^{138},^{138}(d, p)Te^{139},^{139}; Te^{138},^{138} \rightarrow I^{138},^{138}$. Process (2), which is known to occur on the basis of relative intensities, is the usual type of reaction: $Te^{138},^{138}(d, n)Te^{138},^{138}$. Conclusive proof of this identification and interpretation has been furnished by the extraction of the 8-day iodine from tellurium which has been bombarded with neutrons. We cannot as yet state the period of the radio-tellurium from which this iodine grows.

Absorption measurements on the negative electrons emitted by the 8-day iodine indicate a maximum energy of 0.9 Mev; a gamma-ray is also present.

We have irradiated iodine with the fast neutrons from a lithium plus deuterons source and confirm the 13-day period reported for the same bombardment by Tape and Cork, who surmised it to be due to $I^{138}$. We have chemically identified this activity as an iodine isotope, so that the assignment to $I^{138}$ appears to be definite. (The antimony fraction of this same bombardment was inactive, while the tellurium precipitate exhibited a 10-hour half-life which can be ascribed definitely to $Te^{139}$. This tellurium period has been reported previously, following neutron and deuteron bombardment of tellurium, but without definite isotopic identification.)

The yield of the 8-day iodine from $Te(d, n)I$ is very much larger than that of the strongest 13-day iodine that, we have been able to produce by the reaction $I^{138}(n, 2n)I^{139}$.

This research has been aided by grants from the Research Corporation, The Chemical Foundation and the Josiah Macy Jr. Foundation.

J. J. LIVINGOOD
G. T. SEABORG

Radiation Laboratory, Physics Dept. (J. J. L.)
Chemistry Department (G. T. S.),
University of California,
Berkeley, California,
June 1, 1938.
the biological oxidations and their relationship to the thyrotoxicosis need further study.


Chesney, Clawson and Webster, and Marine, Spence and Rosen, and others, have observed marked hyperplasia in the thyroids of rabbits fed a cabbage diet. Suk has reported large nodular goiters occurring endemically in a community where cabbage is a principal dietary item. The goitrogenic factor in cabbage has been reported to be certain cyanide compounds found in cabbage and other members of cruciferae family. Subsequently goiters have been produced in experimental animals treated with sodium cyanide, potassium cyanide and methyl cyanide. Robinson and O'Hare, and Barker and Hare have reported the development of goiters in hypertensive patients being treated with sodium or potassium thiocyanate.

We are reporting certain metabolic studies and the thyroid history of one patient who developed a goiter after one year's treatment with potassium thiocyanate administered in treatment of hypertension. The blood cyanate during the period of treatment varied between 3.8 mgm. per cent and 8.9 mgm. per cent. While following the prescribed regimen, the patient improved symptomatically and the blood pressure fell from 220/130 to 140/100 mm. Hg. However, after taking the thiocyanate for one year, the patient complained of swelling in the neck. The swelling was found to be a large goiter over which a loud bruit could be heard. The gland was estimated to weigh about 180 grams. A definite bilateral lid lag and exophthalmos were present. The basal metabolic rate was minus 17. Blood plasma iodine was at the level of myxedema. A biopsy taken from the gland, which at operation was very vascular, disclosed extreme hyperplasia with architecture resembling papillary cystadenoma. The cyanate therapy was stopped, and one month later the thyroid was of normal size and the basal metabolic rate and blood plasma iodine had returned to normal levels.

We feel that the paradoxical findings in this case, i.e., the extreme hyperplasia in the gland, but laboratory signs of hypothyroidism, are of interest and may be of fundamental importance in interpreting thyroid physiology.

Recent Clinical Developments in the Therapeutic Application of Radio-Phosphorus and Radio-Iodine. By Joseph G. Hamilton (by invitation) and John H. Lawrence, Berkeley, Calif.

Radio-phosphorus has been employed for the treatment of a group of patients with polycythemia vera during the past two and a half years. A marked remission of the clinical and hematological signs of this disease has been observed in the majority of the patients following the administration of radio-phosphorus. No evidence of either leukopenia or anemia has been observed in any of the patients and none developed any symptoms of radiation sickness.

A series of experiments with radio-iodine have been undertaken with the collaboration of Drs. Mayo H. Soley and Karl Eichorn. In these studies, a series of rabbits and two dogs were given large doses of radio-iodine (1st half-life 8 days) and it was noted that almost complete destruction of the thyroid took place in all of the animals without evidence of damage to the other tissues of the body. Later, much smaller doses of radio-iodine were administered orally to three patients with hyperthyroidism. Four to six weeks later a marked clinical improvement was noted in each of the patients, with a parallel approach of the basal metabolic rate to normal levels. No adverse effects from the radio-iodine were noted either during or after the administration of this substance. Four and a half months later two of the patients were in a state of complete clinical remission and the third required another small dose of radio-iodine.


Previous publications of this series have dealt with tracer studies in animals and man. Our present report is a preliminary one which gives an account of our early experiences, both failures and successes, in an attempt to evaluate the possibility of using radioactive iodine in a practical clinical manner in the treatment of patients with Graves' disease. It is in the nature of a progress report on this work up to date.

The general plan of the treatment is described and an analysis of the 10 (or more) cases in which it has been tried is given.

Information which we have obtained by careful study of the radioactive iodine uptake by the goiters and the urinary excretion studies is presented and discussed in relation to the problem of finding the best means for the administration of this new therapeutic agent.

A Chemical Test for the Differentiation of Adrenocortical Tumor from Hyperplasia is Markedly Masculinized Women. By Harry B. Friedrich (introduced by Samuel A. Levine), Boston, Mass.

Previously reported observations from this laboratory are in general accord with those recorded by others in that the total 24-hour urinary 17-ketosteroid (17-KS) excretion is above 45 mgm. of crystalline androsterone in cases of virilizing adrenocortical tumor, and from 15 to 35 mgm. in instances of adrenogenital syndrome due to adrenocortical hyperplasia. Two cases of hyperplasia have been encountered, however, in which the 17-KS excretion equaled that found in tumor cases; and in one of these, which was a striking example of pseudoludermaphroditism, the 17-KS excretion was more than 80 mgm. Thus it is not the total 24-hour 17-KS excretion which is of significance in differential diagnosis. A differential point may have been found, however, excretion closed in the total cortical to than half

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DELIGHTED TO TELL YOU THAT YOU WERE ELECTED TO THE SOCIETY
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sine, appears to take place in either cell or follicular lumen. The point of practical importance is that very soon after the administration of radioactive iodine, most of the radio activity is to be found in the lumen of the follicle, and in delineating the mechanism involved in this type of radio therapy, one should consider that the thyroid cells are being bombarded by beta rays originating from within the follicle. This situation is greatly in favor of radio iodine as a cruiser. Beta rays have a low penetrating power, as they originate...
March 20, 1946

Dr. J. H. Means
15 Chestnut St.
Boston, Mass.

Dear Dr. Means:

We are in receipt of a considerable amount of correspondence relative to the use of radioactive iodine in the treatment of Graves' disease, and also two papers. (One by Hertz and Roberts and the other by Chapman and Evans.) I would be very much interested to have from you a statement as to the actual status of this situation as you see it, since apparently you have had the opportunity to read both manuscripts.

There seems to be some difference of opinion among the authors as to the exact status of the cases involved in the report.

Very truly yours,

[Signature]

Is
RADIOACTIVE IODINE IN THE STUDY OF THYROID PHYSIOLOGY

VII. The Use of Radioactive Iodine Therapy in Hyperthyroidism

SAUL HERTZ, M.D.
Boston
and
ARTHUR ROBERTS, Ph.D.
Cambridge, Mass.

In previously published experiments of this series, radioactive iodine was used as an indicator in the study of animal and human thyroid physiology and iodine metabolism. Much of this preliminary work was done with a view to the discovery of the conditions under which radioactive iodine might be administered with maximum radiational effect in the pathologic thyroid of patients ill with hyperthyroidism. The present paper is a progress report on our early experience (1941-1946) with such "internal irradiation" in the treatment of 29 cases of hyperthyroidism. It is, indeed, a three to five year follow-up report on these cases.

PROCEDURE

Patients were selected who had no previous iodine treatment and who were judged clinically to have hyperthyroidism. The usual clinical tests were made and the patients were presented to the Thyroid Clinic of the Massachusetts General Hospital for diagnosis and determination of their condition.

THE TREATMENT OF HYPERTHYROIDISM WITH RADIOACTIVE IODINE

EARLE M. CHAPMAN, M.D.
and
ROBLEY D. EVANS, Ph.D.
Cambridge, Mass.

Roentgen treatment has been used for hyperthyroidism for many years. In 1923 Means and Holmes pointed out that in this form of treatment about one third of the patients are cured, another third improved and another third not affected. Since 1923 ordinary iodine by mouth has been used as a preoperative method of quieting the hyperactive thyroid in preparation for surgery. Under iodine alone occasionally the patient and the doctor have been agreeably surprised to find that the symptoms and signs of hyperthyroidism disappeared, and a permanent remission apparently was effected. That x-ray treatment and iodine treatment sometimes cure hyperthyroidism led to the hope that some day a more effective, nonsurgical agent would be found. Then the MacKenzies and Astwood discovered that several chemical compounds inhibit the function of the thyroid in hyperthyroidism as well as under other circumstances. Several of these agents have been...

...aided in part by a grant from the John and Mary R. Markle Foundation.

From the Thyroid Clinic of the Massachusetts General Hospital (Dr. Chapman) and the Radioactivity Center of the Department of Physics of the Massachusetts Institute of Technology (Dr. Evans).


PRODUCTION OF TRACER AND THERAPEUTIC RADIOISOTOPES has been heralded as one of the great peacetime contributions of the uranium chain-reacting pile. This use of the pile will unquestionably be rich in scientific, medical, and technological applications.

Manhattan Project scientific, technical, and administrative personnel have, since the inception of the pile, been cognizant of its peacetime potentialities and have, since the end of the war, been active in attempting to realize these opportunities. Since, however, war-built piles and wartime researches had other objectives, a considerable transition in researches, developments, and operations connected with piles must be effected before the supply of radioisotopes can begin to meet the demand.

COMMENTS ON AVAILABILITY OF RADIOISOTOPES

1. A pile cannot make the extensive variety of radioisotopes producible with the cyclotron because the cyclotron makes use of a much greater diversity in energy and type of nuclear bombarding projectiles. Present piles are copious sources of low-energy neutrons, which can give rise to large yields of isotopes produced by \((n,f)\) and \((n,\gamma)\) processes.

2. Although large numbers of radioisotopes are produced in abundance by the fission of uranium in the piles, their availability is limited by the difficulties encountered in isolating them. It has not yet been found feasible to remove individual fission products from waste solutions of the plutonium extraction process. Most of the fission products being made available are not salvaged by-products of the plutonium process but are in each case items requiring special production from unprocessed irradiated uranium.

3. Most of the radioisotopes in greatest demand, such as \(^{14}C\), \(^{35}S\), and \(^{32}P\), must be produced by the irradiation of materials foreign to the pile. Existing piles were not designed for this purpose.

4. Although a pile is a copious source of neutrons, it is not a limitless source. It is possible to load a pile for nonfission product radioisotope production only up to the limit at which so many neutrons are absorbed in the introduced material that the chain reaction ceases even though the control rods are withdrawn as far as feasible. With available pile facilities, this limit does not permit the production of a sufficient quantity and quality of many radioisotopes to meet anticipated national demands. To accomplish this it would very likely be necessary to build piles especially designed for the purpose.

5. Technical problems involved in the irradiation of some materials have been, and will continue to be, responsible for delays in making certain isotopes available by routine irradiation. Examples of such problems are: (a) proper cooling of the material to prevent rupture of the container by its internal action or by the external action of the coolant, with consequent loss of the material and damage to the pile; (b) careful purification to prevent loss of neutrons by absorption in impurities as well as undesirable radioactivity in the irradiated material; and (c) proper distribution of the material throughout the pile to prevent local overheating or undesirable regulation characteristics of the pile.

ORGANIZATION FOR ALLOCATION AND DISTRIBUTION

In accordance with the established custom of the Manhattan Project of seeking competent outside advice and aid on vital scientific matters, such as nonproject distribution of isotopes, Maj. Gen. L. R. Groves asked the president of the National Academy of Sciences to nominate a representative committee of outstanding scientists to recommend policies and aid in establishing arrangements for a desirable distribution of those tracer and therapeutic isotopes available from Manhattan Project facilities. An interim Advisory Committee on Isotope Distribution Policy was formed, two representatives being chosen from each of the major fields of isotope application: Physics—Lee A. DuBridge (chairman), head, Physics Department, University of Rochester, and president-elect of California Institute of Technology, Pasadena; and Merle A. Tuve, head, Department of Terrestrial Magnetism, Carnegie Institution of Washington, Washington, D. C.; Chemistry—Linus Pauling, director, Gates and Crellin Chemistry Laboratories, California Institute
STORAGE OF RADIOACTIVE IODINE IN A METASTASIS FROM THYROID CARCINOMA

A patient with metastatic thyroid carcinoma was studied from the standpoint of storage of radioactive iodine. The carcinoma was of the adenoma malignum type with widespread bone metastases showing colloid follicles, and with no evidence of recurrence of the primary growth removed thirty-five years previously from the thyroid.

A tracer dose of radioactive iodine was given by mouth, and field plots of its distribution were determined by means of a Geiger-Müller counter. The Geiger counts indicated that more of the radioactive substance had been taken up by a metastasis in the right lower femur than by the thyroid gland itself. Other metastases, which, as a therapeutic measure, had been irradiated previously with deep x-ray, failed to take up the radioactive iodine in appreciable amount. The material present in the femoral metastasis and in the thyroid gland could not be washed out of these tissues by the administration of 54 mgm of potassium iodide, which indicates that the radioactive iodine was fixed in both these tissues.

The possibility of the use of radioactive iodine as a therapeutic agent was suggested because the metastasis in the femur had fixed such a large proportion of the material. Accordingly a therapeutic dose of 10 milli-curies of radioactive iodine, mainly of the 12.6 hour period, was given. The femoral metastasis took up about 30 per cent. and the thyroid gland about 6 per cent. of the total amount administered. Radioautographs of the femoral metastasis were made by placing a film on the patient’s thigh and allowing the radiation from the radioactive iodine to darken the film. The position of this metastasis as shown by the Geiger counter and by the radioautographs agreed well with the area of bone destruction shown in the x-ray plates.

About three weeks after the therapeutic dose the metastasis had lost about 85 per cent. of the radioactive iodine, while the thyroid still contained about the same amount as that originally taken up. A tracer dose given a few days after this finding showed prompt uptake by the thyroid gland, but no appreciable uptake by the femoral metastasis. This would suggest that at least the thyroid-like function of the metastasis had been impaired.

The patient is still under observation and a complete report will be made later.

The radioactive iodine was supplied to us through the kindness of Professor E. O. Lawrence, of the University of California, and Professor R. H. Evans, of the Massachusetts Institute of Technology.

Albert S. Keston
Robert P. Ball
V. Kneeland Frantz
Walter W. Palmer
plasma cholesterol level between 200 and 214 mg. per hundred cubic centimeters. The blood iodine on March 24 was 9.4 micrograms per hundred cubic centimeters. Roentgenograms taken on April 21, 1944, showed no detectable changes in the various metastases. The second therapeutic dose of radioactive iodine, 55.4 millicuries of the eight day isotope, was administered on April 28, 1944. Twenty-seven per cent of this dose (13.8 millicuries) was extracted from a twenty-one hour urine collection and readministered on April 29. A second fraction from urine was obtained later (6.3 millicuries) and readministered on April 30. Thus a total of 75.5 millicuries was administered within three days, giving a radiation dose of 18,200 equivalent r to the tumor and 64 equivalent r to the blood. The white blood cell count showed only a slight temporary fall from 6,000 to 4,500, which, in our opinion, was not significant. The basal metabolic rate dropped to zero in about three weeks and remained about this level until March 1945. The plasma cholesterol fluctuated from a level of about 200 mg. per hundred cubic centimeters to a somewhat higher level. The blood iodine level dropped to 6.5 micrograms on June 10, 1944, to 4.7 micrograms on Oct. 7, 1944 and to 5.1 micrograms 5.1 to 41 micrograms per hundred cubic centimeters). Bioassays of the urine for thyrotropic hormone both before and during the interval of this treatment were negative, indicating that the patient's own thyrotropic hormone was inactivated by the tumor tissue.

On March 3, 1945, the third therapeutic dose of radioactive iodine was given. It consisted of 41.6 millicuries of I-131 plus 16.0 millicuries recovered from the urine and fed three days later. The total of 57.6 millicuries gave a tumor dose of 11,600 equivalent r, a blood dose of 41 equivalent r. The patient's weight increased and the basal metabolic rate, which in the normal range immediately before the treatment, dropped to —27 per cent in about three months and has remained consistently low. The plasma cholesterol increased slightly and has remained above the pretreatment level. The blood iodine dropped from 4.1 micrograms per hundred cubic centimeters immediately before this third therapeutic dose to 1.5 microgram per hundred cubic centimeters three months later.

The patient's general condition is good. He moves freely about the hospital and is engaged in occupational therapy.

**Comment**

Adenocarcinoma of the thyroid is generally considered highly radiosensitive. H. F. Hare specifically stated that alveolar carcinoma of the thyroid is not changed histologically by 6,000 r (x-ray). For a successfully treated patient (his case 2) Hare gives the dimensions of the tumor and the interstitial radon dose employed. Calculations show the gamma ray dose to be close to 20,000 r, a value well beyond the reach of external radiation.