Historical Vignette

The Beginnings of Radioiodine Therapy of Metastatic Thyroid Carcinoma: A Memoir of Samuel M. Seidlin, M.D. (1895-1955) and His Celebrated Patient

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SUMMATION

Emerging from a stimulating encounter over fifty years ago between Dr. S. M. Seidlin and a celebrated patient at Montefiore Hospital in New York City are a number of findings that bear significantly on the contemporary practice of medicine relating to targeted radioisotope therapy. In 1943, Seidlin administered radioiodine to this patient, who was hyperthyroid although previously thyroidectomized, but who had several metastases from adenocarcinoma of the thyroid which localized the radioisotope. Seidlin recognized early that some thyroid metastases would take up radioiodine (i.e., function), but only after the normal thyroid gland was ablated, an essential preliminary procedure before radioiodine therapy should be administered, the clinical practice followed to this day. He held that removing the normal thyroid increased TSH production and eliminated the gland's competition for radioiodine, inducing the metastases to function. From 1942 until his death in 1955, Seidlin and his group followed many patients having metastatic thyroid carcinoma, conducting fruitful investigations concerned with the induction of function, dosimetry, and the occurrence of leukemia in some massively treated patients.

Since they figure prominently in the history of targeted therapy with radioisotopes, some historical aspects will be sketched here of the development of the roles played by radioiodine in the diagnosis and therapy of certain types of metastases of the thyroid gland. Radioisotopes of iodine were among the very first of those that are man-made to see clinical application, which dates from the late 1930s. Our account dwells particularly on the pioneering contributions made by the late Samuel M. Seidlin, M.D. (Fig. 1), a practicing endocrinologist and a productive part-time investigator, who played a major role in elucidating and establishing the place occupied by radioiodine for diagnosing and treating metastatic thyroid carcinoma.

Our saga begins in 1942, when Dr. Seidlin, the then Chief of Endocrinology at Montefiore Hospital...
in New York City, was asked to examine patient B.B. (Fig. 2). Although this patient had a complete thyroidectomy nineteen years earlier (in 1923) for "malignant adenoma", with neither thyrotoxicosis then nor hypothyroidism postoperatively, when seen by Seidlin, the patient exhibited surprisingly the classic signs and symptoms of hyperthyroidism, along with severe pain in the lower back. As described by Seidlin and his colleagues, "In October 1939, a pulsating tumor removed from the level of the twelfth thoracic vertebra (Fig. 3) proved to be metastatic thyroid adenocarcinoma (histologically, well-differentiated, with small follicles and colloid). In the next two years his hyperthyroidism increased and roentgenograms revealed new metastases in the lungs, upper part of the right femur, second rib on the left side, left ileum and skull."

To facilitate following our account, it will prove helpful, I believe, to put in perspective some pertinent facts by recalling the state of knowledge in 1942 concerning aspects of thyroid carcinoma and the identity of the then known radioisotopes of iodine. At the time that Dr. Seidlin first met patient B.B., two conflicting papers had been published bearing on the localization of ingested radiiodine by metastases of the thyroid gland. In 1940, Hamilton, Soley, and Eichorn found, from contact radioautographs or autoradiographs (prepared by placing histological sections of the surgically removed thyroid tissue from two patients in contact with photographic film) that, although non-neoplastic regions of the histological sections took up the administered tracer, the adjoining malignant zones were non-functioning; Hamilton and his colleagues concluded, "The failure of cancerous thyroid tissue to acquire appreciable quantities of radio iodine, as shown in these experiments, suggests the impracticality of therapeutic application of this radio element in malignancies of the thyroid." On the other hand, two years later, Keston, et al reported that metastases of the thyroid did store radioactive iodine in one of their patients whose "primary growth had been removed thirty-five years previously from the thyroid".

Starting around the period of World War I, Hevesy and Paneth, experimenting with naturally-occurring radioisotopes, demonstrated that radio-nuclides behaved chemically and biologically precisely as their corresponding stable elements did, so that radioisotopes constitute valuable "radioactive indicators" or tracers, findings that would win
Hevesy the Nobel Prize, recognizing him as "the father of the tracer".

By the mid-thirties many fundamental features of atomic and nuclear physics had been uncovered in rapid succession: Among these signal events were the discovery of the neutron by Chadwick (important for explaining the nuclear structure of isotopes), the invention of the cyclotron in 1932 by Lawrence, the discovery of artificial radioisotopes in 1934 by Joliot and Curie, and immediately thereafter the production of many artificial radioisotopes by Fermi. The radioactive isotope of iodine used in the initial studies which demonstrated uptake by the thyroid gland in 1938 by Hertz, Roberts, and Evans was $^{128}$I, a beta emitter with a half-life of 25 minutes; only relatively small activities of $^{128}$I-about 1/20th of a microcurie(!)-could then be made by Evans, employing the neutrons derived from a radon-beryllium source to irradiate stable ethyl iodide. As is evident, such early methods for the production of radionuclides required the addition of the stable element, so-called "carrier", to assure or facilitate co-precipitation of the radionuclide. Subsequently, carrier-free radionuclides became available, a change that necessitates consideration when interpreting quantitative findings reported in the older literature concerning the determinations of thyroid uptake of radioiodine. It was only in 1938, after the discovery of the 8-day $^{131}$I by Livingood and Seaborg, that enhanced tracer studies of thyroid physiology and pathology became feasible, leading to the development of a large number of invaluable diagnostic and therapeutic procedures applying radioisotopes of iodine -many of these techniques are still widely used. The operation of the first medically dedicated cyclotron at MIT by Evans in 1938 became a source of supply of mixtures of the 12-hr $^{130}$I and 8-day $^{131}$I for many investigators, including later, Seidlin's group at Montefiore Hospital.

It was the uncertainty in the composition of the mixtures of radionuclides that motivated early investigators to use the non-specific terms radioiodine and $I^*$, designations being retained here in describing their initial studies. After 1946, with the operation of reactors supported by the U. S. Atomic Energy Commission, appreciable activities of carrier-free, purer $^{131}$I became readily available -at low cost (thanks to governmental subsidies).

Returning to Dr. Seidlin, who, in 1942 wondered, in view of the conflicting reports in the literature mentioned, just what would be the fate of a radioiodine tracer administered to patient B. B., a daunting undertaking then with the United States at war. After securing the approval of Dr. L. Leiter, Montefiore's Chief of Medicine, and the initial collaboration of L. D. Marinelli, the medical physicist at the neighboring Memorial Hospital (later the Sloan-Kettering Memorial Center), Dr. Seidlin persuaded Dr. R. D. Evans at MIT to produce some $I^*$ for patient B. B., costing Seidlin's research funds about $1500, a considerable sum in those days, long before the coming of NIH grants, control committees, and licenses for nuclear by-products.

In March 1943, patient B. B. ingested his first tracer dose of $I^*$, which revealed localization of radioiodine by all the known lesions plus two previously unsuspected ones (i.e., that they were "functioning"), but no uptake in the neck, the site of the previously excised thyroid gland. This initial survey, made by Seidlin and his colleagues with a hand-held Geiger counter to map the localization of the radioisotope, was a memorable occasion. During the survey, the patient asked that the "machine" be placed on the right parietal part of his head, where he stated there is a pain which "is not a headache";
sure enough, the counter indicated that the radioiodine localized in this site. Subsequently, x-rays confirmed it to be "a fairly sharply circumscribed area of bone rarefaction in the right posterior parietal region". Also attending this session was Dr. David Marine, the Hospital's pathologist, distinguished for his earlier epochal studies of iodine for the prophylaxis of goiter in children of Cleveland. Referring to the audible clicks made by the Geiger counter's register, Dr. Marine stated that he had over the years seen many metastases under the microscope, but this was the first time he heard a metastasis talk!

Since intramuscular injections of thyrotrophic hormone were not followed by the appearance of TSH in B. B.'s urine, Seidlin and his associates conjectured that metastatic thyroid carcinoma inactivated TSH, stemming from Seidlin's earlier research concerning this hormone, a supposition to which we will shortly return. In January 1944, Dr. Seidlin and his group found that they could successfully control this patient's hyperthyroidism, caused by functioning metastases of the thyroid, with thiouracil medication.

Again quoting these authors, "Therapeutic amounts of radioactive iodine were administered orally to this patient between May and October 1943. Definite and lasting clinical improvement followed. In April 1944 and March 1945 additional I* was administered to B. B. with a resultant disappearance of pain, increase in weight and progressive change in all clinical criteria in the direction of hypothyroidism. Roentgenographic evidence pointed to an arrest if not a regression of the disease." Radioiodine therapy was continued and the patient's clinical picture showed striking improvement; the patient's pain in the lesions disappeared and his hyperthyroid state was gradually transformed into one of hypothyroidism, so that the patient developed myxedema and was given desiccated thyroid therapy. Blood curves derived from samples drawn from patient B. B. after receiving therapeutic I* doses permitted making estimates of the radiation dose delivered; thus, these investigators' estimated that over a period of three years, patient B. B. had received nearly 40,000 equivalent roentgens (or about 37,000 rads) to each of his tumors from the administered radioiodine; as will be noted shortly, refined dosimetric determinations were later developed by the group.

In 1949, Dr. Seidlin and his group reported that, "The patient who, six years ago, was bedridden and required opiates, is now moving about freely and has no pain. Roentgenologically, no new metastases have appeared, the pulmonary metastases have completely disappeared and the osseous shadows (lesions?) have shown neither increase nor decrease in size. External measurements with the Geiger counter, which initially showed high readings, have shown no uptake in the past year." Like the other patients having thyroid metastases who followed him at Montefiore Hospital, patient B. B. was studied intensively by Seidlin and his group, employing frequent body surveys to localize functioning sites, as well as in vitro assessment of the activity of samples of urine and blood. Such surveys were performed periodically with our handheld, lead-collimated "directional" Geiger counter, about two days after the ingestion by the patients of test I* doses (circa 1-2 mCi [31]I); these procedures entailing the systematic manual mapping of potential or actual functioning sites, were often correlated with roentgenograms -crude harbinger of the elegant scanning and imaging procedures made feasible by the scanning machines and gamma cameras which came into vogue in the sixties and seventies. The radioiodine content of the urine proved a sensitive and helpful indicator for inferring the retention by the body of the administered radioisotope, providing, of course, that the patient's kidney function was normal. Patient B. B. was unusual among the patients then studied at Montefiore Hospital in having functioning metastases which localized maximal amounts of the ingested I* doses; in accord with such highly functioning lesions, his urinary I* excretion was correspondingly low for a patient lacking a normal thyroid gland (only 30-50% of the administered dose, over the first 72-96 hours).

Although initially B. B.'s lesions were highly functioning, the metastases ceased to take up the administered radioiodine as therapy progressed, concomitant with the patient's clinical improvement. Lesions no longer functioning and his being free of pain, the patient in his later years lived outside the hospital, enjoying financial support from the group's research funds. In May, 1949, following a test dose of radioiodine, an excised skull metastasis obtained from this patient was found to be extensively necrotic with no evidence of viable tumor tissue. Although, as was just stated, no uptake was demonstrable externally by this lesion, the radioautographs prepared of the excised specimen did indicate some
localization of radioiodine, which it was conjectured resulted from the persistent presence of compounds still capable of fixing iodine.\textsuperscript{11}

In 1952, some nine years after the institution of radioiodine therapy, patient B. B. died. An autopsy then revealed widespread presence of an undifferentiated anaplastic type of thyroid tumor, which we speculated resulted from the radiation received by the patient over the years. While there had been no detectable uptake of radioiodine externally as already noted, radioautographs were nevertheless positive.\textsuperscript{12}

Patient B. B. was an intelligent, sensitive, and fiercely proud individual, proving at times a challenge to his caretakers. He properly assessed his value and celebrity, in view of the notoriety he had aroused: Visitors from all over the world streamed to Montefiore Hospital and its basement laboratory to see him and his physician; B. B. even became the subject of an article in \textit{Life} magazine (October 31, 1949). Memorable for me were the numerous instances of Seidlin's sparring, cajoling, and negotiating to gain patient B. B.'s agreement to undergo some clinical procedures or to accede to the demands of the media. I well remember his duelling with Dr. Seidlin, who, failing to get the patient to meet with the photographer for \textit{Life}, was frustrated and disappointed; the following interchange then ensued: Dr. S.: "Is that how you show your gratitude? After all, I cured you of cancer." Patient B. B.: "Dr. Seidlin, you are supposed to be a smart man; if I had cancer five years ago, you know I'd be dead now!"

Soon after administering radioiodine therapy to patient B. B., it became apparent to Seidlin that successful radioiodine therapy depended upon inducing the neoplastic thyroid tissue to function. Two questions needed answering: a) will all histological types of thyroid metastases function, and b) if only certain types can function, under what conditions will this occur? In 1947, Seidlin and his associates\textsuperscript{13} reported their success in inducing uptake of radioiodine in well-differentiated neoplasms of the thyroid gland following thyroidec- tomy or radiation ablation of the thyroid gland by large doses of radioiodine. They found that tumor uptake could also be increased, in some cases, by the injection of thyrotropic hormone (TSH) or by thiouracil medication. Furthermore, Seidlin\textsuperscript{14} concluded that metastases of the well-differentiated, follicular type are likely to become functional; only some tumors of the papillary type will function; but that embryonic, anaplastic metastases hardly ever do so. He speculated that papillary tumors may become functional, since they are often comprised of histological mixtures, including the presence of follicular cells.

\textbf{Figure 4. Left:} Contact radioautograph of an unstained section of metastatic tumor in second rib on the left side (biopsied on November 6, 1943), showing the distribution of radioactive iodine in viable tissue of patient B. B., who had previously been thyroidecomized; darkened area indicates developed photographic grains, the result of exposure to localized \(^1\text{\textsuperscript{3}I}\) by functioning segments of the lesion.

\textbf{Right:} Corresponding photomicrograph of same section as on the Left, stained with eosin and hematoxylin, and at same magnification. Note that the viable regions are dark and the necrotic areas are light; referring to the Left, it is apparent that the uptake of \(^1\text{\textsuperscript{3}I}\) coincides with viable tumor. (Region marked X was shown with higher magnification to have follicular architecture and to contain colloid-like matter in a few follicles; see Fig. 9 of source.) (Reproduced with permission from Figs. 6 and 7, \textit{JAMA} 1946;132:838-847.)
Seidlin\textsuperscript{15} propounded his so-called "TSH hypothesis", namely, that removing or blocking (with thiouracil) the normal thyroid gland increases the production of TSH by the pituitary. In turn, this induces the carcinomatous tissue to become functional, according to its degree of differentiation. Furthermore, he theorized that removing the thyroid gland eliminated competition for the administered radioiodine. The TSH hypothesis enabled Seidlin to resolve the conflict between the findings of Hamilton and those of Keston and Seidlin: Hamilton found no uptake by malignant tissues in the presence of the normal thyroid gland, while both Keston and Seidlin (Fig. 4) were examining metastases in patients after their non-neoplastic glands had been removed.

The TSH hypothesis was the basis for Dr. Seidlin's procedure\textsuperscript{16} for treating well-differentiated malignant lesions of the thyroid: Remove the normal gland by surgery or radioiodine; once function is demonstrated by external counting after the ingestion of a test dose, administer therapeutic activities of radioiodine until function is eliminated - essentially the clinical procedure followed widely ever since. The Montefiore group also advocated that before administering \textsuperscript{131}I therapy, an estimate of the size of the metastasis and of its radioiodine uptake should be attempted to determine the lesion's concentration of the radioisotope, a parameter bearing significantly on the efficacy of \textsuperscript{131}I therapy. For, they held that in order for \textsuperscript{131}I therapy to produce a curacercidal effect, a concentration greater than 0.03 per cent of the administered dose per gram of tumor tissue should be demonstrated; this corresponds to a ratio of at least 30 for the radioiodine concentration in the tumor to that in the blood.

Extending studies of blood radioisotope concentration to many thyroid carcinoma and hyperthyroid patients treated with radioiodine permitted Seidlin and his colleagues\textsuperscript{17,18} subsequently to refine their analysis to yield better estimates of the radiation delivered to the blood, functioning sites, and the whole body. Their computation of the radiation dose delivered to the blood entailed graphical integration to obtain the area under curves of blood radioiodine concentration versus time; they concluded that body radiation from \textsuperscript{131}I is about 50 per cent of that received by blood. Seidlin and his associates\textsuperscript{19} identified an interesting feature characterizing some blood curves: A marked rise in the blood radioiodine concentration, similar to that which takes place concurrently in the radioactivity of the urine, occurred approximately 4-8 days following ingestion of therapeutic doses; this so-called "irradiation produced rise" (IPR) was most pronounced following thyroidectomizing doses and therapeutic doses administered to patients having highly functioning tumors. These IPRs were attributed by Seidlin and his colleagues to the irradiation trauma to the thyroid gland or to functioning thyroid tumor tissue.

Patient B. B. was one of over thirty patients with thyroid carcinoma examined by Dr. Seidlin with radioiodine; of these, sixteen patients with functioning lesions, treated with radioiodine, and followed by Dr. Seidlin comprised the Montefiore Series. For members of the Series, the administered radioiodine ranged from 195 mCi to 2290 mCi over a 6 month-9 year interval. The same clinical procedure outlined earlier was followed for these patients. In addition, corroborative evidence was obtained by assaying the urinary excretion of the administered radioisotope and, if lesions were biopsied, by analysis of radioautographs.

Seidlin and his colleagues\textsuperscript{20,21} reported that two patients of the Montefiore Series succumbed to subacute myeloid leukemia, the occurrence of which the authors discussed in the light of prevailing relevant observations and understanding. The first patient (J.F.) received 13 therapeutic doses of \textsuperscript{131}I from 1947 to 1951, totalling 1455 mCi. It is estimated that he received a cumulative blood radiation dose of about 600 rad; as stated, the whole body dose is about half that of the blood radiation dose. The second patient (B.L.) received 20 therapeutic doses from 1948 to 1953, totalling 1750 mCi of \textsuperscript{131}I, delivering about 550 rad to the blood. The delay in the onset of leukemia occurred, respectively, after 4 and 5 years.

Apart from his involvement with radioiodine and concern with disorders of the thyroid gland, Dr. Seidlin's pioneering efforts before long served as the impetus and inspiration at Montefiore Hospital for collaborative investigations exploiting radioactive tracers, two of which will be cited here. Two dental colleagues were joined by Seidlin and his group to use radioiodine tracers for the study of the physi-
the distribution of fluid solutes in teeth by racliautography.22 He also collaborated with Dr. Emil J. Baumann, the distinguished biochemist at Montefiore hospital, who among other achievements relating to thyroid metabolism, was able to recover 80-95% of the radioactive iodine in the urine resulting from therapeutic doses given to patient B. B., so that it could be re-administered to patients, recycling that effected significant savings for the group's modest research funds. Dr. Baumann expounded the hypothesis that all Group VII elements of the periodic table, having seven valence electrons, would be filtered or localized by the thyroid gland; he and his colleagues confirmed this theory using many radionuclides in experimental animals. As one of the radionuclides studied, it was shown in 1952 by Baumann and his collaborators23,24 that 99mTc as pertechnetate was taken up by the thyroid gland of rats; this is the basis for the current widespread use of the metastable form of technetium, 99mTc, for the imaging of the thyroid gland.

Not long after launching his research with I, Dr. Seidlin established and directed (until his death in 1955) the Medical Physics Laboratory, located in the basement of the Van Cortlandt Pavilion, with the Montefiore Hospital's animal quarters as its immediate neighbor. Despite the many activities it conducted, the Laboratory consisted of one room (circa 80 square feet) and a much smaller 'hot lab' (Fig. 5), created by enclosing the space around a terminating staircase, the latter was the site for the processing and storing of radioisotopes and radioactive urine decaying to appropriate levels. The same hot lab served as a darkroom for the preparation and processing of racliautographs. If modest in area, the Laboratory, we were told more than once by Dr. Paul Aebersold, the then Chief of the Isotopes Division of the U. S. Atomic Energy Commission, was nevertheless the largest consumer of 131I. In addition to conducting the clinical studies of metastatic thyroid carcinoma with radioiodine outlined here, many more patients were diagnosed and treated with 131I for hyperthyroidism and other thyroidal disorders in the Laboratory; this experience and its documentation were incorporated subsequently into several investigations and publications.25-27 Not only were clinical procedures performed by the Laboratory, it also hosted many visitors and provided training to physicians, physicists, and technicians from all over the world.

Although Seidlin devoted half-time to the Laboratory and other hospital duties, for which he received no financial compensation from Montefiore Hospital (a common circumstance at a voluntary teaching hospital in the days before Medicare), he was responsible for securing financial support for
the Laboratory's operations and its personnel. He met these obligations by obtaining monetary gifts from his patients and friends, awards from private agencies, and meeting deficits from his own pocket, an arrangement which eased in the fifties, with the coming of NIH extramural grants and the Hospital assuming the costs of non-research clinical services performed by the Laboratory.

After Dr. Seidlin's death, the Laboratory was given much larger quarters and greatly expanded its scope, offering the hospital many other clinical procedures using radioisotopes as they were developed, as well as conducting a variety of investigations involving collaboration with many of the Hospital's services, training many residents and visitors, making it an early active nuclear medicine service. I cannot conclude this historical sketch of Dr. Seidlin and his contributions without alluding to some of his special personal traits. Apart from his outstanding professional and scientific attributes, Dr. Seidlin was highly cultured, charming, and a gifted linguist. Possessing a highly infectious sense of humor, he was an engaging conversationalist and an entrancing raconteur. Dr. Seidlin enjoyed the friendship of scientific and clinical peers and the adoration of his patients, many of whom were celebrated and enjoyed great renown. As I hope this account makes manifest, he was a persistent and determined scientist and clinician, not readily deterred by obstacles and difficulties. Particularly memorable about the pursuit of Seidlin's scientific ventures were his extraordinary insight, his uncanny intuition, and his unflinching insistence on rigor and accuracy. He frequently stated to us two of his favorite expressions: "Don't assume anything!" and "In science there are no miracles or mysteries, only ignorance that in time will give way to knowledge and understanding." It was my singularly good fortune to work closely in many of these endeavors with Dr. Seidlin from 1948 until his death in early 1955, greatly enriching and profoundly influencing my life, and, surely, affecting similarly many others with whom he interacted.

REFERENCES


About the Author...

Currently, Edward Siegel, Ph. D. is an Adjunct Professor at the Department of Radiology, University of California, San Francisco. In 1948, S. M. Seidl, M. D., the then Chief of Endocrinology and the Medical Physics Laboratory at Montefiore Hospital in New York City recruited Siegel, who served as the Physicist-in-Charge of the Medical Physics Laboratory from 1949 to 1962; following the demise of Dr. Seidl on January 2, 1955, Siegel directed the Laboratory.