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Kenneth E. W. Melvin

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The Calcitonin Assay and Multiple Endocrine Neoplasia Type 2 Syndromes: Historical Footnote

Kenneth E.W. Melvin, MD*

To describe the circumstances surrounding the first case of medullary carcinoma diagnosed by means of calcitonin assay offers the opportunity to pay tribute to two individuals whose work has contributed greatly to our understanding of the multiple endocrine neoplasia type 2 (MEN-2) syndrome: Professors Dilwyn Williams and Armen Tashjian.

In 1967, not long after arriving at the Tufts New England Medical Center, I encountered a patient with pheochromocytoma and a thyroidectomy scar. Five years with Dr. Williams at the Hammersmith Hospital had prepared me for such an encounter. In short order, study of the sections from this patient's thyroid gland, and from his mother's before him, established that the earlier diagnosis of undifferentiated thyroid carcinoma had to be changed to medullary carcinoma. Mindful of Dr. Williams' speculation two years earlier that medullary carcinoma might ultimately prove to be a calcitonin-secreting tumor, I approached the three groups in Boston who were then performing bioassays for calcitonin. Only Dr. Armen Tashjian, then at the Harvard School of Dental Medicine, thought the idea worthy of putting to the test. Blood was duly obtained, and two weeks later Dr. Tashjian reported excitedly that the patient's serum was strongly hypocalcemic in the bioassay system. Subsequent studies (1) quickly established the identity of the hypocalcemic principle as calcitonin.

Within a year of that first observation of hypercalcitonemia in a patient with medullary carcinoma of the thyroid (MTC), two events of great consequence occurred. First, Dr. Tashjian perfected his radioimmunoassay for calcitonin, and second, a healthy young man in his early twenties, quite unrelated to the earlier patient, consulted me for an examination because of his concern that so many aunts and uncles had required operations for neck tumors. Although his neck examination was entirely normal, his family history was almost too good to be true. Accordingly, he was recruited as both family spokesman and sleuth, and surgical specimens dating back several years were gathered from various hospitals throughout Massachusetts. The thyroid tumors that had been removed over the previous decade were all medullary carcinomas, although none had been so diagnosed.

With the support of Dr. Edwin Astwood, the clinical research unit at the New England Medical Center was placed at my disposal for a study of nearly one hundred members of the kindred, all of whom resided in Weymouth, Massachusetts. In order to sell the idea to the family members, a local church hall was hired, and invitations were sent to the entire kindred. To my surprise, everyone turned out for the occasion, and the women even served refreshments. The notion that blood tests both before and after a calcium infusion might permit the diagnosis of a cancer affecting perhaps 50% of those present resulted in 100% participation.

Within a few weeks the first family member produced an abnormal calcitonin response to the infused calcium load. He was a young, vigorous corporate executive with nothing abnormal to be felt in his neck, and absolutely no phenotypic or symptomatic abnormality to suggest his underlying disease. Understandably, therefore, he regarded with chagrin and much skepticism our suggestion that he have his neck explored. No assurance could be offered to him other than that he was the first, and in terms of what his participation might offer to the rest of his family, he could become a hero.

It is a tribute also to Dr. Harry H. Miller, Chief of Oncologic Surgery at the Tufts New England Medical Center, that his investigative curiosity and faith in his medical colleagues led him to agree to perform that thyroidectomy solely on the indication of a serum chemical abnormality of unproved validity.

As the patient entered the operating room on that day in 1969, his immediate family and several other relatives gathered in the anteroom anxiously awaiting the outcome. The fate of the entire study depended upon finding a tumor. Although exposure of the thyroid gland revealed nothing abnormal, Dr. Miller was able to palpate a nodule in each lobe of the gland and proceeded with the total thyroidectomy. It was a moment of great elation when the excised gland was sectioned sagittally...
to reveal the characteristic bilateral nodules of medullary carcinoma. Within the year, 12 of the 97 members of the kindred had undergone thyroidectomy for occult medullary carcinoma. On the first anniversary of the initial family meeting, a reunion held in the same church hall was a very festive occasion. In the subsequent 15 years, the studies have continued (2). Dr. Graze, with his colleague Dr. Gagel (present at this conference) and others, have published their findings in 35 cases of MTC in that kindred of 105 (3).

Remarkably, the threads of this story also have an international origin. This kindred in Massachusetts is related directly to the equally large kindred studied in Sweden since 1969 by Dr. Margareta Telenius-Berg. Her results in 105 members of the Swedish kindred were presented at this symposium and are included in this journal issue (4). It is altogether fitting that the scientific bonds that enjoined our interests more than a decade ago should culminate in the bonds of friendship stimulated by this first international meeting on MEN-2.

References


