Multiple Endocrine Neoplasia Type 2 Syndromes: Historical Perspectives

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John H. Sipple, MD*

Eponyms are flattering, sometimes embarrassing, and certainly not descriptive. When I was asked to give the historical perspective on the Sipple syndrome at this conference, I was flattered. The paper I wrote in 1959 was my only venture into endocrinology, and I have worked in the field of pulmonary disease for the last 25 years. So much outstanding work has been done by so many investigators in this field, and my contribution was so minimal, that remembering the name MEN-2 is more meaningful to a medical student than remembering an eponym.

Discovery of the Sipple Syndrome

I was a medical resident in 1959 when I was asked by the neurosurgical service to consult on the case of a 33-year-old man who was hypertensive after he had surgery for arteriovenous malformation of the brain with cerebral hemorrhage. I thought his hypertension was due to increased intracranial pressure; but, as I stood at the autopsy table, I was amazed when I saw large, bilateral pheochromocytomas and a 2 cm pale tan mass in each lobe of the thyroid gland and nodular enlargement of the only parathyroid gland we could find. Microscopically, the thyroid tumors, called follicular adenocarcinoma (1), were invasive and poorly differentiated. Since this was the same year in which Hazard first described medullary carcinoma (2), it was no wonder that our pathologists did not recognize it as such. The pheochromocytomas had high levels of epinephrine and norepinephrine, so there was no doubt that they were functional. Since we did not have serum calcium or phosphorus determinations, we did not know whether the patient had hyperparathyroidism.

As I stood at the autopsy table, I knew I was looking at something special although I did not understand it. I doubted very much that it was a chance occurrence. When I went to the literature, I found only a 1952 book by DeCourcy and DeCourcy entitled Pheochromocytoma and the General Practitioner (3). They stated that "a considerable and, we believe, a significantly high percentage of patients with pheochromocytoma have had coexistent diffuse or nodular goiter or thyroid carcinoma." That was interesting, but it provided no facts. So I dug deeper in the library stacks and was able to find five other cases of carcinoma of the thyroid in patients with pheochromocytoma. All were quite similar to the case I had seen, mainly young adults with bilateral pheochromocytomas and anaplastic-appearing carcinomas of the thyroid. All five cases had been reported because of some interesting medical or surgical aspect of pheochromocytoma and not because of the presence of thyroid carcinoma. At that time, there were slightly more than 500 cases of pheochromocytoma in the literature. The six cases of carcinoma of the thyroid were somewhere between 14 and 40 times the expected incidence if it were a chance occurrence. No familial history of pheochromocytoma or carcinoma of the thyroid was reported in any of the six cases, although a few cases of familial pheochromocytoma had been reported by that time. It was well known that 5% of the patients with pheochromocytoma had neurofibromatosis. Pheochromocytoma had also been described in some of the inherited neurocutaneous syndromes in which vascular malformations in the brain occurred. The clue which should have led me to suspect that my patient’s problem was hereditary was that he had an arteriovenous malformation in the brain. It seemed reasonable that pheochromocytoma and neurofibromatosis might be an inherited condition because both tissues arise from neuroectoderm, but I could not understand how carcinoma of the thyroid gland would fit into that scheme.

In my literature search I found experimental data to suggest that fluctuating levels of catecholamines might cause fluctuating levels of thyroid-stimulating hormone (TSH), which might cause alternating hyperplasia and involution of thyroid follicular cells, which in turn, might result in carcinoma of the thyroid gland. So I wrote a three-page paper entitled “The Association of Pheochromocytoma with Carcinoma of the Thyroid Gland,” submitted it to the American Journal of Medicine, and it was published in 1961 (1).
Medullary Carcinoma of the Thyroid

The association I reported in 1961 was developed into a well-defined syndrome by Cushman from Rochester, New York, in 1962 when he reported a family in which the father had pheochromocytoma, medullary carcinoma of the thyroid, and parathyroid adenoma; the son had pheochromocytoma and medullary carcinoma of the thyroid; and the granddaughter had medullary carcinoma of the thyroid gland (4). Cushman correctly concluded that the syndrome was a Mendelian dominantly inherited disorder and that the carcinoma of the thyroid gland was medullary (MTC), not a carcinoma of the follicular cells.

In our case, the pathology had been reviewed by Dr. Schimke, and the carcinoma was medullary (5), as it was in all subsequent reports.

Dr. Anton Joachimpalli and Dr. Phillip Speller in Syracuse are the endocrinologists who studied the relatives of the patient I reported. The family pedigree was prepared by Dr. Joachimpalli (Figure). Both children of the propositus had pheochromocytoma and MTC, as did one of his brothers. Two of the brother's children had MTC, and one had C-cell hyperplasia. A seven-year-old grandchild has elevated calcitonin levels and is awaiting thyroid surgery.

The fascinating work of defining the nature of MTC began in 1959 when Hazard described this entity as a solid and nonfollicular carcinoma (2). Amyloid could be identified consistently in the stroma. The incidence of lymph node metastases is high, and the carcinoma appears undifferentiated under the microscope but is not highly malignant. Usually called papillary or anaplastic carcinoma before Hazard's description, MTC accounts for only about 5% of thyroid carcinomas. About 20% of cases are familial, and most of the familial cases occur in MEN-2 kindreds (8).

Discovery of Serum Calcitonin as a Marker for MTC

In 1966, Williams reported that the parafollicular cells in the thyroid are the cells of origin of medullary carcinoma (9). In his studies, Pearse (10) found evidence that, in response to elevated serum calcium, these cells secreted a serum calcium-lowering hormone which he called thyrocalcitonin. In 1968, three reports confirmed calcitonin secretion by MTC (11-13), and by the early 1970s, Tashjian and associates developed a radioimmunoassay for the hormone in serum (14-16). Serum calcitonin was measured before and after calcium infusion in 170 members of kindreds with MEN-2. In 47 subjects whose calcitonin tests were positive, 42 had thyroidectomies, and all had C-cell abnormalities; 35, medullary carcinoma; and 7, C-cell hyperplasia. Thyroid nodules or palpable lymph nodes could be demonstrated in only half of the cases. Thereafter, other families with MEN-2 were discovered by calcitonin tests performed on relatives of patients thought to have sporadic MTC or sporadic or familial pheochromocytoma. Thus was discovered a very sensitive and specific tumor marker.

Calcitonin testing and thyroidectomy in patients with MEN-2 disclosed that the C-cell abnormality is a rather diffuse process. The carcinomas are almost always bilateral, and areas of C-cell hyperplasia are frequently adjacent to areas of carcinoma. Occasionally, in younger patients, only C-cell hyperplasia is present, indicating that it is a precursor of medullary carcinoma.
The chromaffin cells in the adrenal medulla are the precursors of pheochromocytoma. Although the very high incidence of bilateral pheochromocytoma in MEN-2 had been appreciated since the early 1960s, it was not until 1975 that adrenal medullary hyperplasia was reported as a precursor to pheochromocytoma in MEN-2 (16,17). Apparently MEN-2 is characterized first by hyperplasia and then by neoplasia of C-cells of the thyroid gland and of the chromaffin cells of the adrenal medulla.

Ljungberg’s demonstration of a positive chromaffin reaction to chromate by MTC cells prompted speculation that C-cells may have the same embryological origin as the chromaffin cells of the adrenal medulla, ie, from the neuroectoderm (18). However, C-cells arise from the ultimobranchial body (6th branchial pouch), which is endoderm. It has been suggested that some neuroblastic cells may migrate to the ultimobranchial body (19).

Two other topics merit attention: One is the parathyroid gland and the relationship of MEN-1 to MEN-2; the other is the patients with MEN-2 who also have mucosal neuromas but hardly ever have parathyroid disease (MEN-2B).

Parathyroid Hyperplasia
Parathyroid hyperplasia or adenoma with or without hyperparathyroidism is a definite feature of MEN-2, although not generally very important clinically. I think it is an independent part of the inherited disease and not a result of hypercalcitonemia, because a number of cases with hypercalcemia have been reported, and one case with normal calcitonin had parathyroid hyperplasia (7). The common denominators of MEN-1 and MEN-2 are parathyroid disease and Mendelian dominant inheritance.

MEN-2 Patients with Mucosal Neuromas
In 1965, Williams reported two patients with pheochromocytoma and MTC who had mucosal neuromas (20). Other similar cases were described, some with skeletal abnormalities; and in 1975, Sizemore’s group (8) suggested the subset MEN-2B to distinguish these cases from those kindreds without mucosal neuromas (MEN-2A). The Table, slightly modified from a 1975 article by Block, et al (21), uses Sizemore’s suggested classification and the currently accepted terminology. In 1981 Carney, et al reported 21 cases of MEN-2B (22). All had MTC, and six had pheochromocytoma. Twenty had typical facial characteristics with big lips, elongated face, wide-eyed expression, and broad-based nose; and 16 were marfanoid and asthenic. All had some skeletal abnormality, most commonly, pes cavus, kyphoscoliosis or lordosis. Apparently no overlap occurs between MEN-2A and MEN-2B kindreds.

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<th>Type 1 (Wermer syndrome)</th>
<th>Type 2</th>
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<tr>
<td>Pituitary tumors</td>
<td>2A Medullary thyroid carcinoma (MTC)</td>
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<td>Pancreatic islet tumors</td>
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<td>Zollinger-Ellison syndrome</td>
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<td>Parathyroid tumors</td>
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| 2B Medullary thyroid carcinoma (MTC) |
| Pheochromocytoma |
| Rarely parathyroid disorders |
| Other associated abnormalities |
| Mucosal neuromas |
| Hyperplastic corneal nerves |
| Skeletal anomalies |

Conclusion
Since my original case report in 1961, so many individuals have contributed to our understanding of MEN-2 that it is impossible to recognize them all in this short historical overview. It is gratifying that my name has been associated with this syndrome, but it is even more rewarding to participate in a workshop like this. This First International Workshop on MEN-2 illustrates that observations in one case can lead to the contributions of many workers in the field.
References