Ann Surg Oncol
https://doi.org/10.1245/s10434-024-15079-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – GLOBAL HEALTH SERVICES RESEARCH

Jeffrey A. Norton and the Multiple Endocrine Neoplasia Syndromes

Samuel A. Wells Jr, MD

Department of Surgery, Washington University School of Medicine, St. Louis, MO

ABSTRACT

Background. Jeffrey A. Norton could have been a professional football player but instead he chose to pursue a career in medicine and in the process became an outstanding academic surgeon. This story recounts his ascent from a small town in Massachusetts to the pinnacle of academic surgery.

Methods. After graduating from high school in Albany, New York, Jeff continued his education at Dartmouth University, the State University of New York Upstate Medical University at Syracuse (SUNY Upstate Medical University), and the Department of Surgery at the Duke University School of Medicine. When he completed the surgical residency, he spent 10 years at the National Cancer Institute (NCI) where he and his colleagues made significant contributions to the diagnosis and treatment of patients with endocrine tumors. After leaving the NCI, he had highly productive years as a Professor in Departments of Surgery at Washington University, the University of California at San Francisco, and Stanford University. He became a member of every major academic surgical society and won numerous awards for his accomplishments in research. His expertise in educating medical students and surgical residents is legendary.

Results. In addition to his academic accomplishments, Jeff trained legions of young surgeons who subsequently made significant contributions in surgical investigation and clinical surgery.

Conclusion. It is most fitting that the Stanford University School of Medicine has assembled a group of Jeffrey Norton's colleagues in academic medicine and surgery to pay tribute to his achievements as a surgical scientist.

Stanford University School of Medicine, Symposium Honoring Jeffrey A. Norton, MD, 13 October 2023.

First Received: 2 February 2024
Accepted: 8 February 2024

S. A. Wells , Jr MD
e-mail: wellss@wustl.edu

Published online: 17 March 2024

IN THE BEGINNING

Jeff Norton was born in Pittsfield, Massachusetts, and while still a youngster, his family moved to Albany, New York, where his mother was an administrative assistant at the State University of New York at Albany and his father was the manager of a Texaco fuel distribution center on the Hudson River.

He graduated from Christian Brothers Academy in Albany where his academic record ranked him third in his class. He played football, basketball, and baseball. He was captain of the football team and at graduation received the Thom McCann award as the best football player in the Albany area. He was named to the Christian Brothers Hall of Fame in 1965.

In addition to a strong academic record at Dartmouth, he was captain of the soccer team and defensive right tackle on the football team. At graduation he received the Timothy Wright Ellis award as the most outstanding student athlete at Dartmouth.

Jeff went to medical school at the State University of New York Upstate Medical University at Syracuse (SUNY Upstate Medical University) and after graduation he moved to North Carolina to begin an internship in the Department of Surgery at Duke University School of Medicine. After 2 years as an intern and resident he joined me in the laboratory, where he developed an interest in surgical oncology and endocrinology. He then spent 3 years in the Surgery Branch of the National Cancer Institute (NCI), two as a Clinical Associate and one as an Investigator, before returning to Duke to complete the surgical residency. He then returned to the NCI for 10

years, where he became a Senior Investigator, and from 1986 to 1992 he was the Head of the Surgical Metabolism Section. Jeff took advantage of the vast resources and opportunities available to National Institutes of Health (NIH) investigators, and through tireless work in the laboratory and the clinic, he made significant contributions.

During his years at the NIH, Jeff Norton's progress was facilitated by his association with four internationally known scientists. Murray Brennan, currently Sir Murray Brennan, was Head of the Surgical Metabolism Section of the Surgery Branch when Jeff arrived as a Clinical Associate in 1976, but he departed in 1981 to join the faculty of the Memorial Sloan Kettering Cancer Center (MSKCC) in New York. He became Chairman of the Department of Surgery there in 1985, a position he held for 20 years. During Jeff's early tenure at the NCI, his research interests paralleled those of Murray's, and being a quick learner, he mastered the necessary clinical and laboratory techniques that led to substantial research productivity in surgical endocrinology and oncology.

John Doppman, the Head of Diagnostic Radiology at the NIH Clinical Center, was an excellent clinical and investigative radiologist, but his greatest contribution to his colleagues in the Surgery Branch was his skill in locating endocrine tumors that had eluded detection during one or more prior surgical explorations. Doppman was the last court of call for patients whose endocrine tumors could not be found during surgery, and it was said at the NCI and elsewhere, "*If John Doppman could not locate an endocrine tumor, no one could*". His expertise made life easier for surgeons and their patients until the year 2000 when he retired after being at the NIH for 28 years.

Jeff also had a close association with two physicians at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and worked with them in the management of patients with sporadic and hereditary endocrine tumors. Robert Jensen was the Chief of the Gastrointestinal Cell Biology Section of the Digestive Disease Branch in the NIDDK and the world's authority on the management of patients with Zollinger–Ellison (ZE) syndrome. Physicians throughout both the United States and foreign counties referred their complicated patients with ZE syndrome to him.

Steven Marx, the Chief of the Genetics and Endocrinology Section of the NIDDK, was an expert endocrinologist whose major interest was the management of patients with familial and sporadic endocrine tumors. He made numerous contributions to endocrinology, particularly the diagnosis and management of patients with Multiple Endocrine Neoplasia Type 1.

METHODS: THE MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

Multiple Endocrine Neoplasia Type 1

In 1954, Paul Wermer, a physician on the clinical faculty at the Columbia College of Physicians and Surgeons in New York City, described a family with the autosomal dominant inheritance of tumors of the parathyroid glands, the pancreatic islets, and the pituitary glands. This constellation of hereditary endocrinopathies came to be known as Multiple Endocrine Neoplasia Type 1 (MEN1).[1] In 1997, Settera Chandrasekharappa at the National Human Genome Research Institute of the NIH and his associates cloned the MEN1 gene, which codes for a protein, menin, a tumor suppressor gene, with unclear function.[2] There are over 1600 genetic mutations in the MEN1 gene but there is no correlation between a single mutation, or a group of mutations, and the clinical expression of disease.

Of patients with MEN1, 90% have hyperparathyroidism, 80% have neuroendocrine tumors of the pancreas or duodenum, 50–65% have tumors of the anterior pituitary gland, and a lesser number have adrenal adenomas, bronchopulmonary, thymic, or gastric neuroendocrine tumors. The islet cell tumors in the pancreas or the duodenum secrete gastrin, which stimulates the stomach to secrete hydrochloric acid, resulting in severe ulceration of the stomach and duodenum. In 1985, Zollinger and Ellison described the clinical picture associated with tumors of the pancreatic islets, and the entity became known as the Zollinger–Ellison (ZE) syndrome.[3] Numerous patients with the ZE syndrome were admitted to Dr. Robert Jensen's service in the NIDDK, and many of them were then referred to Jeff Norton for surgical treatment. Although surgical resection is the only cure for parathyroid hyperplasia or pancreatic islet cell tumors, the outcome is guarded in patients with MEN1 because the tumors are multicentric and often incompletely resected.

In 1999, Jeff was the first author on a classic paper describing the treatment of 151 patients with ZE syndrome.[4] Surprisingly, 49% of the islet cell tumors were in the duodenum, 36% were in the pancreas, 11% were in lymph nodes, and 9% were found at other sites There were no cures following surgical treatment of patients with ZE syndrome and MEN1, but 34% of patients with sporadic islet cell tumors were disease-free at 10 years after surgery. Whether the tumors were sporadic or hereditary, the 10-year overall survival was 94%.

Multiple Endocrine Neoplasia Type 2

In 1952, John H. Sipple graduated from Cornell University in Ithaca, NY, and in 1955 he graduated from the Cornell College of Medicine in New York City. From 1955 to

1959, he completed an internship and residency in Internal Medicine at the SUNY Upstate Medical University, followed by a fellowship in pulmonary medicine at the Johns Hopkins Hospital from 1961 to 1962. He then joined the faculty in the Department of Internal Medicine at SUNY Upstate Medical University.

During April of 1959, Sipple had been the Chief Medical Resident at the Syracuse VA Medical Center where he cared for a patient who died from a hypertensive crisis shortly after admission. At autopsy, the patient was found to have a brain hemorrhage, bilateral pheochromocytomas, and bilateral thyroid tumors, which, on microscopic evaluation, were diagnosed as *"poorly differentiated, invasive, follicular adenocarcinoma of the thyroid"*. Sipple published an account of his patient and five other patients found on a literature search. All six patients had bilateral pheochromocytomas and bilateral thyroid tumors with thyroid pathology described variously as papillary carcinoma, adenocarcinoma, or anaplastic carcinoma.[5] In 1959, investigators at the Cleveland Clinic brought clarity to the thyroid pathology conundrum when they described medullary thyroid carcinoma (MTC), a neoplasm with unique histological characteristics, which differed from thyroid carcinomas reported previously.[6] In 1968, clinical investigators at the Albany Medical Center Hospital published a description of a large kindred with MTC, pheochromocytomas, and hyperparathyroidism. They named the syndrome Multiple Endocrine Neoplasia Type 2[7] and suggested that the entity described earlier by Wermer be named Multiple Endocrine Neoplasia Type 1.

In 1984, clinical investigators at the Henry Ford Hospital in Detroit were preparing a symposium on endocrinology and bone metabolism when a sharp-eyed physician planning the meeting noted Dr. Sipple's 1961 paper and invited him to participate in the symposium, which he did. The title of Sipple's talk published subsequently was 'Multiple Endocrine Type 2 (MEN2) Syndromes. Historical Perspectives'.[8] In Dr. Sipple's final publication,[9] he and his colleagues identified the *RET C634R* mutation as the cause of the MEN2 syndrome affecting his patient identified in 1961. As a result of Sipple's 1961 paper, the characterization of MEN2, as Sipple's syndrome, stuck and clinicians today often use that term in describing MEN2. This is unfortunate, since rightfully, the MEN2 syndrome should be known as the Steiner, Goodman, Powers syndrome.

The MEN2 syndromes are caused by mutations of the *RET* proto-oncogene, and there is a relation between genotype and phenotype. The MEN2 syndrome is further characterized as either MEN2A or MEN2B, and virtually all patients with these syndromes develop MTC and 50% develop pheochromocytomas. Additionally, 25% of patients with MEN2A develop hyperparathyroidism. Patients with MEN2B do not develop hyperparathyroidism, but they have a characteristic physical appearance with a typical marfanoid habitus, including characteristic facies with neuromas on mucosal surfaces.[10] The MTC that develops in patients with MEN2B is highly aggressive, developing at a young age and metastasizing early. Jeff Norton was the first to notice the highly aggressiveness character of MTC in patients with MEN2B, compared with the behavior of the tumor in patients with sporadic MTC or MEN2A.[10] Children at risk for MEN2 can be screened at birth to determine if they have inherited a mutated *RET* allele, in which case they are candidates for prophylactic thyroidectomy, where the thyroid gland is removed before MTC develops or while it is confined to the thyroid gland. Jeff was a member of the team that first demonstrated the benefit of prophylactic thyroidectomy in children from MEN2 families who had inherited a mutated *RET* allele.[11]

RESULTS

Jeff was the first author or senior author on several papers concerning the management of patients with both MEN1, MEN2, and sporadic endocrine tumors. His published work done in collaboration with Drs. Brennan, Doppman, Jensen, Marx, and other senior and junior investigators at the NIH, defined the standard therapy for the diagnosis and treatment of patients with sporadic or hereditary endocrine tumors.[12–18]

Besides Jeff's accomplishments in basic and clinical investigation, he participated in training many Clinical Associates in the Surgery Branch of the NCI, including Steven Lowry, Jeffrey Moley, John Skibber, Robert Udelsman, Douglas Fraker, Martha Zeiger, Gerald Doherty, Sally Carty, and others. His research and clinical achievements were recognized by his receiving the NIH Director's Award on 27 June 1990, *"For your commitment to excellence as an accomplished and innovative laboratory researcher and as a highly skilled and competent surgical oncologist"*. His research accomplishments were also recognized by his colleagues in the American Surgical Association, who awarded him the Flance–Karl award in 2012 for *"Achievements in translational research that have transformed the surgical approach to endocrine neoplasms."*

In 1992, Jeff joined the faculty as Professor of Surgery and Chief of Endocrine and Oncological Surgery in the Department of Surgery at Washington University. He was also the Associate Director of the Washington University Comprehensive Cancer Center. In 1997, he moved to the University of San Francisco as Professor of Surgery and Vice-Chairman of the Department of Surgery, and in 2003 he became Professor of Surgery, and the Chief of Surgical Oncology at the Stanford University School of Medicine. In 2006, he was named the Robert and Mary Ellenburg Professor of Surgery and the Chief of General Surgery.

In additions to Jeff's contribution to surgical endocrinology and oncology, he also demonstrated excellence in the education of medical students and residents. From 1998 though 2002, while at the University of California at San Francisco, Jeff won the Chief Resident Teaching Award, or the most outstanding teacher in Surgery. His excellence in teaching continued when he moved to Stanford, where in 2005, 2007, 2008, and 2020 he received either the Excellence in Teaching Award or the Chief Resident Teaching Award. In 2006, he received the John Austin Collins, MD, Memorial Award for outstanding teaching in Surgery at Stanford, and in 2011 he received the Alwin C. Rambar-James BD Mark Award for Excellence in Patient Care at Stanford University Medical Center.

CONCLUSION

Jeff Norton is a surgical hero. I say that not so much for the contributions that he made to the management of patients with neuroendocrine tumors but because of the type of person he is and how he lived his life. He is a role model for all of us.

DISCLOSURES The authors declare that they have no conflict of interest.

REFERENCES

1. Wermer P. Genetic aspects of adenomatosis of endocrine glands. *Am J Med*. 1954;16:363–71.
2. Chandrasekharappa SC, Guru SC, Siradanahalli C, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science*. 1997;276:404–7.
3. Zollinger RM, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. *Ann Surg*. 1955;142:709–23.
4. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger–Ellison syndrome. *N Engl J Med*. 1999;341:635–44.
5. Sipple JH. The association of pheochromocytoma with carcinoma of the thyroid gland. *Am J Med*. 1961;31:163–6.
6. Hazard JB, Hawk WA, Crile G Jr. Medullary (solid) thyroid carcinoma of the thyroid; a clinicopathology entity. *J Clin Endocrinol Metabol*. 1959;19:152–6.
7. Steiner A, Goodman AA, Powers SR. Study of a kindred with pheochromocytoma, medullary thyroid carcinoma, hyperparathyroidism, and Cushing's disease: multiple endocrine neoplasia type 2. *Medicine*. 1968;43:371–408.
8. Sipple JH. Multiple endocrine type 2 syndromes. Historical perspectives. *Henry Ford Hosp Med J*. 1984;32:219–22.
9. Hughes JM, Sipple JH, MacGillivray DC, et al. The sipple syndrome: from clinical description to genetic analysis in the index family. *Endocrinol*. 1996;6:427–30.
10. Norton JA, Froome LC, Farrell RE, Wells SA Jr. Multiple endocrine neoplasia type IIb. The most aggressive form of medullary thyroid carcinoma. *Surg Clin N Am*. 1979;59:109–18.
11. Wells SA Jr, Chi DD, Toshima K, et al. Genetic and clinical studies in the multiple endocrine neoplasia type 2 syndromes. *Ann Surg*. 1994;220:237–50.
12. Norton JA. The use of high-resolution ultrasound to locate parathyroid tumors during reoperations for primary hyperparathyroidism. *World J Surg*. 1987;11:579–85.
13. Norton JA, Cornelius MJ, Doppman JL, et al. Effect of parathyroidectomy in patients with hyperparathyroidism and Zollinger–Ellison syndrome and multiple endocrine neoplasia. Type 1: a prospective study. *Surgery*. 1987;102:958–66.
14. Doherty GM, Doppman JL, Miller DL, et al. Results of a multidisciplinary strategy for management of mediastinal parathyroid adenoma as a cause of persistent primary hyperparathyroidism. *Ann Surg*. 1992;215:101–6.
15. Norton JA, Doppman JL, Collen MJ, et al. Prospective study of gastrinoma localization and resection in patients with Zollinger–Ellison Syndrome (ZES). *Ann Surg*. 1986;204:468–79.
16. Perry R, Neiman L, Cutler G. Primary adrenal causes of Cushing's syndrome: diagnosis and surgical management. *Ann Surg*. 1989;210:59–68.
17. Krampitz GW, Norton JA. RET gene mutations (genotype and phenotype) of multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma. *Cancer*. 2014;120:1920–31.
18. Doppman JL, Miller DL, Chang R, et al. Intraarterial calcium stimulation test for detection of insulinomas. *World J Surg*. 1993;17:439–43.