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From the laboratory bench to the operating room: the role of the surgeon in cancer prevention

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Abstract

BACKGROUND: The last 200 years have seen remarkable achievements in the art and clinical practice of surgery. These advances include the introduction of antisepsis, anesthesia, vascular anastomosis, antimicrobials, organ transplantation, and the widespread application of minimally invasive operative procedures. Very recently, a surgical procedure has been shown to cure diabetes, representing the most effective treatment of a metabolic disorder by surgeons.

METHODS: The author reviewed the major surgical milestones in the modern surgical era and prepared this monograph for presentation as the Claude H. Organ, Jr. Memorial Lecture at the 68th Annual Meeting of the Southwestern Surgical Congress.

RESULTS/CONCLUSIONS: This address summarizes the story of medullary thyroid carcinoma and multiple endocrine neoplasia type 2, an archetype for a surgical procedure to prevent cancer development.

The last 200 years of the modern surgical era have seen great achievements in the care of the sick, encompassing not only the correction of crippling injuries and serious acquired maladies, but even the prevention of disease.[1] The growing technical ability and desire of surgeons to attempt complex operations in the early 19th century far exceeded the limits of physiology and fortitude of most patients to tolerate their early ambitious efforts. The major obstacles to successful surgical procedures were the absence of antiseptic practices, and the lack of availability of effective methods for providing anesthesia and pain relief. These deficiencies did not allow patients to tolerate the brutal and radical intervention of opening the body and attempting to extricate or sever the diseased part. Nevertheless, early surgeons proved bold and unfaltering in their efforts to intervene despite the seemingly insurmountable risks.

Physicians and surgeons from the Egyptian dynasties 16-17, dating from the 17th century BC, placed sutures and applied treatments with grease, honey, or fresh meats as medicinal poultices. Accounts of their practices are found in the earliest surgical treatise on military trauma, the Edwin Smith Papyrus. Overcoming the challenges encountered to allow the opening of a body cavity or severing of

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an extremity without generating uncontrollable bleeding or inevitable sepsis must have seemed almost unachievable. Eventual unraveling the mysteries of human anatomy and physiology was a requirement for the establishment of the surgical discipline, but progress came slowly, including detailed human anatomic dissections by Andreas Vesalius (*De humani corporis fabrica*) in 1543, and the description of the circulation of the blood by William Harvey in 1628. Distinguished and accomplished physicians in the late 18th century, such as Scottish surgeon John Hunter, relied on careful observation and applied the scientific method to provide early surgical interventions.

In light of these historical obstacles, the earliest successes of surgeons in the modern era are incredible achievements that are therefore difficult to imagine: the removal of a 22-pound ovarian tumor from a Kentucky woman by Dr. Ephraim McDowell on Christmas day in 1809 before the availability of anesthesia; the rapid life-saving amputation of an extremity with an irreparable vascular injury, complex fracture, or festering infection in a Civil War soldier that is at the same time horrific and merciful. Remarkable technical achievements followed including the pioneering work of Alexis Carrel, who essentially developed and performed all of the foundational techniques of vascular surgery in experimental animals between 1901 and 1910, and received the Nobel Prize in 1912 for his work in devising the methods to suture blood vessels together and perform grafts. Successful transplantation of organs into man followed. Dr. Joseph E. Murray and Dr. John Hartwell Harrison, in collaboration with nephrologist Dr. John P. Merrill, performed the first successful kidney transplant between identical twins at Peter Bent Brigham Hospital in Boston in 1954. Although Dr. Thomas E. Starzl performed the first human liver transplant at the University of Colorado in 1963, the lack of effective immunosuppression limited its success. His tenacity prevailed and more effective immunosuppressive medications enabled successful liver transplantation 4 years later. Landmark achievements in cardiac surgery ensued rapidly during the mid-12th century, notably successful operation on the nonbeating heart and development of cardiopulmonary bypass by John Gibbon 1953, and the first human heart transplant in a grocery worker in Cape Town, South Africa by Dr. Christiaan Barnard in 1967. In addition to the availability of antimicrobials and effective immunosuppressive drugs, the rapid expansion of techniques for minimally invasive operative procedures arguably stands as one of the most significant advancements of the surgical craft in the latter portion of the 20th century.

A very recent significant achievement for surgeons is the effective correction of a metabolic disease with an operative procedure. It has now been established that Roux-en-Y gastric bypass or sleeve gastrectomy, provides superior cure of type 2 diabetes when compared with intensive medical therapy.[2] Just a short time ago, the notion that a surgical procedure would allow "cure" for a metabolic disorder may have seemed a little like the musings of space travel in 1900. However, this achievement is now a reality. This very short history of surgical milestones is provided to reflect on the exponential progress that has occurred in the last 200 years of the modern surgical era.

With the background of these historical signposts of achievement, it is meaningful to consider the evolution of advancements that have resulted in the performance of an operation to prevent cancer from ever developing or removing it while still in situ. This intervention can now be offered to selected patients that have been afflicted by their inheritance with an almost certain fate of malignant change in a specific organ. The remarkable story of medullary thyroid carcinoma (MTC) includes a progression of discoveries relating to the embryology, histopathogenesis, biochemistry, and molecular genetics of the disease. It is particularly cogent to reflect also on the strong contribution of surgeons to the important discoveries that underlie the development of a "prophylactic" or preventative surgical intervention for MTC. These discoveries included the recognition that medullary carcinoma arises from the C cells of neural crest origin, the identification of the MTC tumor cell's hormone product calcitonin and development of a sensitive radioimmunoassay for its measurement as a tumor marker, the elucidation of specific genetic mutations underlying the molecular oncogenesis and familial associations of MTC, the perfection of a complex procedure for safe thyroidectomy and appropriate lymphadenectomy in pediatric patients, and finally targeted therapies for patients with metastatic or unresectable disease.

The essential features of a disease for which an early operative intervention intended to prevent future cancer development is best suited include: (1) a strong genetic predisposition to cancer development conferred by the inheritance of a specific mutation in the germline; (2) the availability of a DNA mutation screen to accurately identify disease allele carriers with a simple and reliable diagnostic test that can be performed at any age; (3) a disease natural history that puts the individual at a risk for malignant progression sufficient to warrant an invasive surgical procedure that does not carry an inordinate risk of adverse clinical consequences, and for which there is no better alternative therapy; (4) the ability to completely and safely remove the target organ(s) at risk with a resultant high success rate in preventing the subsequent development of invasive cancer; (5) an effective medication or treatment to replace the function of the organ removed; and (6) a reliable tumor marker or screening test to detect persistent or recurrent disease. You et al[3] defined prophylactic surgery for cancer prevention as "the pre-emptive operative removal of an organ before malignant transformation or while the cancer is in situ". Dr. Samuel A. Wells, Jr., my surgical mentor, is a pioneering endocrine surgeon scientist who has provided seminal contributions to the understanding of this disease spanning its entire evolution of discovery. Dr. Wells has also enumerated the important characteristics of a hereditary cancer syndrome that make