Discurso de investidura como Doctor "Honoris Causa" del Excmo. Sr. Luther W. Brady

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The Evolution of Medicine and Radiation Oncology—Selected Life Time Memories and Modern Challenges

With the identification of x-rays in November of 1895 by Roentgen and the subsequent presentation of that work to the Academy of Medicine in Würzburg, there was almost immediate recognition that x-rays had a significant and important biological effect. It was proposed by Professor Emil Herman Grubbe in Chicago, Illinois, that it be used to treat a lady with carcinoma of the breast done on 26 January 1896, with a positive objective response. The first patient to have been cured using x-rays was in 1899, and with the preparation of radium by the Curies' in 1898, the first patient to be treated by a combination of external beam radiation therapy and radium was reported by Wright at the Memorial Sloane Kettering in New York.

The initial investigations were directed at a single fraction that might maximize potential for cure. However, this lead to major and significant complications as a consequence of treatment. It was not until the early 1920s with the reports from the American Hospital in Paris by Baclesse that the present schematics of fractionation and protraction were proposed, based on treatment of carcinoma of the vocal cord, with excellent responses and with long term cures, with little in the way of major side reactions from the treatment. The next years were redirected toward identification of the unit of measurement from Roentgen to rem to rad, and ultimately to Centigray. During that time, there was the major evolution and development of instrumentation, ranging from 110 kilovolts to 200 to 250 to 400 kilovolts for treatment of cancer. It was not; however, until the early 1940s that the first cobalt unit was put into practice in Toronto, Canada, with the work being done by Harold E. Johns. The second cobalt unit was installed at the Lankenau Hospital, in Philadelphia, and ultimately at the M. D. Anderson Hospital in Houston. The Linear Accelerator was developed and released

for clinical use in the late 1950s, early 1960s, after there had been work done with the Van der Graff generator.

The advent of the new Linear Accelerator offered greater homogeneity of the radiation dose being delivered to the tumor, and with major significant reduction in the side effects relative to treatment. In the early 1980s, there was a major push to develop dynamic treatment planning and treatment delivery. This was funded by the National Cancer Institute, but resulted in the fact that computers and technology were not available to do three-dimensional reconstructive treatment planning and treatment delivery.

Three-dimensional conformal treatment began in the late 1980s and the early 1990s, intensive modulated radiation therapy technologies were introduced with the advent of better systems for immobilization, rotational devices, and energies in the range of 10 to
20MEV. This lead to significant and important advances in terms of treatment. In 2016, more than 60% of all patients with malignant disease are patients with cancers of the breasts, prostate, colo-rectal and lung. The results from these advances in radiation therapy have led to more than 95% of patients of cancer of the prostate being cured, more than 96 or 97% of patients with cancer of the breasts, more
than 80% of patients with colo-rectal lesions, but still, only 15% overall of patients with cancer of the lung.

The Cyberknife was developed some 12 years ago, allowing for more precise definition of the volume to be treated, with computer control and minimizing the dose to viable structures in the immediate area, with margins that could be created in 3 mm or less. A large increasing number of patients have been treated on Cyberknife with excellent results and with major reduction in side effects, but with the very major advantage of hypofractionation of the treatment being delivered in 1 to 5 fractions, rather than the 30 to 40 fractions generally speaking used for definitive care.

In 1985, Kohler/Milstein received the Nobel Prize for their work in producing antibodies to human cancer cells. The Wistar Institute in Philadelphia embarked upon a program of preparing a series of monoclonal antibodies, we cooperated with them in doing the work that allowed for translation to a clinical area of treatment. One of the most exciting antibodies was anti-epidermal growth factor monoclonal antibody, which we used in treatment of patients with primary high grade gliomas of the brain. With glioblastoma multiforme, the ordinary expected survival is 12 months or less, and with anaplastic foci, 24 months or less. However, with the combination of

surgery, radiation therapy, and the antibody, the median survival for glioblastoma multiforme was 26 months and for anaplastic foci 76 months.

At the point that the project began, there was absolutely no interest in doing immunotherapy in the United States. That was not true to the same degree in Europe. Now there is overwhelming interest every day of one after another new antibody in terms of treatment either independently or in combination with chemotherapy.

With the emerging new technologies in diagnostic radiology and the ever increasingly sophisticated development of radiation therapy instruments, we are now able to do precision treatment with very precise identification and treatment of the tumor and sparing the normal tissues in the surrounding area with margins of 3 mm or less.

The greatest mention in *The New York Times* of treatment from various institutions in the United States report we now have not one treatment for cancer, but one million treatments for cancer based on the new developments in genomic identification of the tumor and developing treatment programs, with genetic abnormalities.

The situation in the United States at the moment is one of not only increased precision in terms of treatment, a greater reliance of multidiscipline management with radiation, chemo and antibodies, but also an emphasis set forth by greater emphasis on genetic profiles.

These are exciting times with many new investigative endeavors being pursued. Thirty years ago, the thought of being cured from cancer in general was 25% and today that number is 75% or better.

In spite of these advances; however, there is hard work ahead to maximize the potential to take advantage of not only genomic data, but more elaborate programs for precision treatment and greater reliance on combinations of treatment, including not only chemotherapy but also antibodies. The future looks brighter than ever before.

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