科技资料

The Role of High Energy Electrons in the Treatment of Cancer

25th Annual San Francisco Cancer Symposium, San Francisco, Calif., February 9–11, 1990

The Role of High Energy Electrons in the Treatment of Cancer

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To Thomas Karger

The 25th San Franscisco Cancer Symposium and its proceedings are dedicated as a Festschrift to commemorate the 60th birthday of Thomas Karger.

Thomas Karger is President of S. Karger AG, whose firm under his direction has published all of the past symposia proceedings as well as this, the twenty-fifth. Without Thomas Karger's foresight and imagination, this oncological series would not have been possible.

We, in Oncology, are indebted to you, Thomas Karger.

Foreword

'The Role of High Energy Electrons in the Treatment of Cancer' was the theme of our 25th Annual San Francisco Cancer Symposium. This was also the subject of our Second Annual San Francisco Cancer Symposium in 1966. At that time, the majority of electron generators – Betatrons and Linear Accelerators – were located in universities and large medical centers. Today, most of the electron generators are linear accelerators which are in wide distribution throughout the world; indeed there are over one thousand machines in the United States alone. These accelerators are located not only in medical centers, but in community hospitals and free-standing installations. It is imperative that those utilizing this new generation of accelerators be familiar with and knowledgeable about the physical, radiobiological and clinical aspects of high energy electrons.

On February 10 and 11, 1990, some of the world's acknowledged authorities in the radiobiology/physics and clinical applications of high energy electrons joined us in San Francisco for this Silver Jubilee. The presentations and discussions formed the basis of this 25th volume of *Frontiers in Radiation Therapy and Oncology* published by S. Karger AG. We hope this text will update the information available to us today and enable us in the future to better apply this exciting modality in the treatment of cancer.

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We are indebted to Cullyn Marie Vaeth, Aurore Vaeth and Karen Freitas, who as in years past, gave so generously and devotedly, their time and talents to make possible this Silver Jubilee of the San Francisco Cancer Symposium.

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Introduction of Dr. Juan A. del Regato

Gene Haynes: It is a real privilege and an honor to be the host of this luncheon meeting for so many outstanding figures of radiation oncology. Jerry, we wish to honor you with a scrapbook commemorating 25 years of a great deal of effort producing this symposium as well as maintaining an outstanding residency training program which you nutured for 30 years. There are many radiotherapists you have trained, over 50 of them, who say, 'I'm in radiation therapy today because of your devotion to training'. It's been a real privilege and honor for Dottie and me to make a scrapbook of your history, from your residents who love you, here's a scrapbook of a lot of history.

Jerome M. Vaeth: Thank you Gene and Dottie and the many contributors to this book.

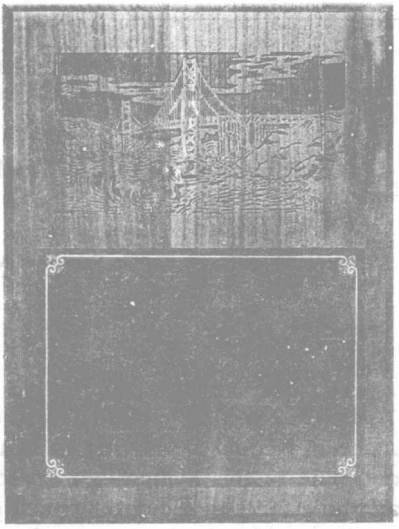
John Meyer: We all look forward to Dr. del Regato's talk, but first I would like to make a presentation, one that I have been looking forward to, and I think many others have been looking forward to as well. Over the past 9 years in my participation in this symposium I have seen some extraordinary contributions to it, to its mission to give a time and a place for the strongest voices in oncology to be heard. I have to think first of the speakers over the past 25 years who have been generous with their time and generous with their intellectual talents. Some 280 contributors to the symposium volumes over the past 25 years have given us a review of the spectrum of current oncology problems. I have to think of the Vaeth family that has been absolutely resolute in their support of this symposium, Jerry's wife, Rory, and his daughter, Cullyn. Each year they spend literally weeks of their time attending to the details of this symposium and the family often has to cover some of the expenses of the symposium themselves. The symposium, in fact, has never really paid for itself by registration fees, but has survived by the generosity of many strong benefactors, e.g., Varian Corporation, Haynes Radiation Ltd., and many others who have sup-

ported. First and foremost, though, the symposium would not exist without its founder, without its tireless champion, Jerry Vaeth. Over the years all of the plagues of rising costs, scheduling possibilities, political changes, ill health, all of this, I think, would have conquered a lesser man. I think all credit must go to Jerry for his perseverance in continuing this symposium which he and which we all value so highly. I am very proud to announce the endowments of the Annual Jerome Vaeth Lecture to the San Francisco Cancer Symposium. The contributions for this have, in fact, come from everywhere in and almost seemingly universal ovation. All of the residents who graduated from the St. Mary's Program have contributed. Many of the current and prior speakers have contributed. I have received sizable contributions from Karger Publishers, and Varian Corporation, as well as especially generous gifts from Drs. Richard Bettenhausen, Don Eads, Bernie Lewinsky, Charles Prather, George Schwartz, Ed Sacks, and Steve Mann. All told nearly 80 contributors, especially coming from so many of his peers, I think this is a greater tribute to Jerry than I can possibly say. It is also a guarantee of the continuation of this symposium in the highest possible quality.

Jerry has always held in greatest esteem Dr. del Regato and I think it is only fitting, and Dr. del Regato has agreed, to present a plaque to Dr. Vaeth.

Juan A. del Regato: Dr. Vaeth, it seems to me that it was not long ago when you abandoned your initial training in gynecology and came to us, enthusiastically embracing your training in Therapeutic Radiology at the Penrose Cancer Hospital of Colorado Springs. Yet, they tell me that you are about to retire; you must have aged very rapidly! It was our privilege to share with you our professional experience and I am now offered the additional one of presenting to you this handsome plaque. Your friends wish to commemorate the fact that you came to San Francisco and through sustained effort established the fastest growing cancer center in the US west coast, moreover, you created this San Francisco Cancer Symposium that has been held for 25 consecutive years and that you have trained a good number of radiotherapists who are a persisting credit to your educational efforts, as well as to St. Mary's Hospital. I simply wish to add that I take pride in you and in your accomplishments as my own.

Jerome M. Vaeth: I am touched, of course. What more can I say? I want to thank you for joining us for this luncheon meeting, hosted by Dottie and Gene Haynes of Haynes Radiation Ltd. Dottie and Gene, over the years, have been our loyal friends. They were there with moral and monetary support at a time when our symposium was threatened with extinction 5 years ago. The luncheon today is just still another example of their generosity. Thank you Dottie and Gene.



Dr. del Regato is our guest speaker. He is my mentor, my role model. He is the father of American radiotherapy. He founded the first residency in our specialty. At the time when he did this, residents were trained in general radiology and practiced both diagnostic and therapeutic radiology. Many of you radiotherapists know the name Ralston Paterson of Manchester, England. He once said that the American radiologist is most unique because he is trained in both radiation therapy and diagnostic and thus he is bilaterally incompetent. I was a product of the 'straight' radiation therapy program of Dr. del Regato's, as were Bill Moss, Vic Marcial, and many others to follow. My residents who are here today, past, and present, are, therefore, progeny of this man. He is a brilliant and innovative teacher, as well as superb clinician. He is an author of the classic textbook, *Cancer*, and this book remains the Gold Standard by which all subsequent texts must be appraised. I once saw this motto on the side of a New York sausage truck, 'often imitated, but never equalled,' which epitomizes Dr. del Regato's textbook, *Cancer*. He founded our specialty organization, ASTRO. Dr. del Regato inspires others to imitate. I am a reasonably good imitator. Most of my ideas of Department organization, of my training program, and indeed my combativeness when anybody confronts me in attempt to deter me in a cause that I believe in, are clones of his influence. These symposiums, 25, are patterned after Dr. del Regato's cancer seminars, all 24. He taught me to find a good oncological subject, select a talented faculty and recruit it, publish the proceedings, and above all persevere in this endeavor (even though it pains you) year after year after year. An important part of Dr. del Regato's seminars were the rousing cocktail parties at the Broadmoor Hotel. His seminars had class and worldwide recognition. Varian Associates with Rory Vaeth's management hosts our version of Dr. del Regato's reception. Please join us tonight for this reception.

Dr. del Regato, I am honored, as are all of us, that you would fly from Florida, the opposite side of the United States, to address us. We are your grateful offspring. Dr. del Regato will speak to us on 'Milestones in Therapeutic Radiology'.

Vaeth JM, Meyer JL (eds): The Role of High Energy Electrons in the Treatment of Cancer. Front Radiat Ther Oncol. Basel, Karger, 1991, vol 25, pp 4–9

Milestones in Therapeutic Radiology

J.A. del Regato

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Dr. Vaeth kindly asked me to come to this meeting to talk at this luncheon. I could not say no to him yet wondered what I could possibly contribute to this Symposium. I decided to simply remind you of some early milestones in the development of our specialty.

As you know, it was on the night of November 8th, 1895, that Roentgen discovered the new rays which, not knowing what they were, he called X-rays; the designation has stuck. The announcement of the 'photography of the invisible' was made to the world, through cable, on January 8th, 1896. Emil Grubbé (1875–1960) a medical student in Chicago who manufactured Crooke's tubes, promptly acquired an induction coil and proceeded to take radiographs of his and other peoples' hands. Two weeks later he went to a faculty meeting of his homeopathic school and showed to his professors his reddened hands. One of his mentors applying some homeopathic logic concluded that if these rays could cause such 'pathogenic condition' they should be able to treat disease. Thus, before the end of January of 1896, and barely over 2 weeks after the news of the discovery, a patient, Mrs. Rose Lee with cancer of the breast was referred to Grubbé. He irradiated her daily for several weeks in his shop in an alley behind LaSalle Street. Unfortunately her records were lost in a flood of the City of Chicago [8].

In Nashville, John Daniel, a professor of physics, upon learning of the invisible rays proceeded to take the radiograph of his minister's hand. He then reflected on the opportunity of looking into the mystery of the brain. He looked for a brainy fellow, and who better endowed than the Dean of the Vanderbilt Faculty of Medicine whom he talked into posing for a prolonged exposure since the tubes were weak. And nothing came out of it except Dean Dowell's hair: first radiation epilation over observed and carefully and chronologically annotated by Daniel for publication in April 1896 [4].

The impact of Roentgen's discovery was great: during that first year more than 1,000 papers and over 50 books were published on the subject of X-rays. Thor Stenbeck (1864–1914), a Swedish pioneer of radiology, is credited with being the first to cure a patient with cancer of the skin with X-rays in 1899 [16]. Francis Williams (1852–1935), contemporary, in Boston [20] presented cured cases of carcinoma of the lower lip to the Boston City Medical and Surgical Society. Photographs of patients treated for cancer of the skin and lower lip were later published in Dr. Williams' Book, 'The Roentgen Rays in Medicine and Surgery', which appeared in 1901 [31, 32].

It took months of laboratory efforts, tons of chemicals, of water and of minerals for Pierre and Madame Curie to produce their first milligrams of radium which were given to Professor Henri Becquerel (1852–1909); he placed them in his vest pocket and after a couple of weeks noticed the reddening of his skin. Pierre Curie (1859–1906) verified the effects on his own forearm and gave the next few milligrams to Henri Alexander Danlos (1844–1922) to study its effects on various skin conditions including cancer. Danlos developed the earliest gadgets for brachytherapy [19, 30].

In 1902, a charismatic radiologist of Vienna, Guido Holzknecht (1872–1931), produced the first device for the measurement of radiations which he called a 'chromoradiometer', based on the color changes caused by their exposure to X-rays [9]. He also established a unit 'H' for 'Haut' (skin); it was used for many years until the 1930s when we figured it was equivalent to about 100 roentgens [17].

In 1903, a remarkable observer, Hermann Heineke (1873–1922), a surgeon of Leipzig, described the effects of irradiation of lymphoid structures. His detailed account has never been improved upon [7, 22].

In 1903, Heinrich E. Albers-Schoenberg (1865–1921) of Hamburg placed a capsule of radium in the cage of guinea pigs and observed that although they continued to have coitus the females were not impregnated [1].

Claudius Regaud (1870–1941), a notable histologist of Lyon, France, with sound knowledge of the substraton of spermatogenesis, irradiated the testes of rats and observed that the maximum affects took place on the most embryonic cells of the line, the spermatogonia, and the spermalocytes, spermatids and spermatozords were less affected as they became more differentiated [20]. Already in 1905, Regaud pointed out that the differential effect between the undifferentiated and the mature cells could be taken advantage of in the irradiation of malignant tumors [14].

Isolated workers in Europe and in the United States had made empiric attempts to use radium in the treatment of accessible tumors. In 1910, Louis Frederic Wickham (1861–1913) and Paul Degrais (1874–1954)

published a book in Paris, which was translated and printed in New York and London, 'Radium Therapy' [30]. The book gave great impulse to the uses of radium for the treatment of malignant tumors; it contained the earliest gadgets devised for the purpose of brachytherapy as well as an account of techniques and results.

In 1913, William Duane (1872–1935) became the first professor of bio-physics at Harvard; he had been a professor of physics at the University of Colorado and had spent 6 years as an associate of Marie Curie (1867–1934). Duane developed a radium emanation (radon) extraction and purification plant. He also originated the radon 'seeds' for implantation into tumors, an idea first suggested by Alexander Graham Bell (1847–1922) in a letter to the editor of *Nature* [19]. A theoretical physicist of note, there is evidence that Duane's ideas were made use of by subsequent workers of Nobel stature [21].

It is important to recognize that it was the development of radiotherapy that made evident the need of special institutions for the diagnosis, treatment and research in the field of cancer. At the start of World War I there were already three leading institutions: The Radium Institute of Paris under Mme. Curie and Regaud, the Radiumhemmet of Stockholm, under Gösta Forssell (1876–1950) [16] and the Memorial Hospital of New York, under James Ewing (1866–1943) [15]. These three institutions, primarily concerned with the treatment of cancer under euphemistic titles, worked out their own approaches to the association of surgery and radiotherapy.

During World War I (1914–1918), radiodiagnosis made the greater strides while still struggling with gas tubes, transformers and interrupters. Radium therapy was hampered by the scarcity and high cost of the radioactive element (about $100,000 per gram). Following the war, the development of the cascade transformer by Frederich Dessauer (1881–1974) of Frankfurt [18], the valve rectifiers and the mechanical rectifier by Walter Snook (1897–?) of Philadelphia, and the hot cathode tube by William Coolidge (1873–1975) of Schenectady, opened the way for what was called 'deep therapy' for roentgentherapy of internal tumors. It was only 180–200 kV but it was all that was available for more than a decade and was sufficient to permit remarkable results. Evidence of the progress achieved may be found on the early reports on the treatment of cancer of the cervix collated by the Committee on Radiology of the Commission on Cancer of the League of Nations.

In 1922, Regaud, then Co-Director of the Radium Institute of Paris, tried to find what was the single dose that would sterilize the testis of the experimental animal; he gradually raised the dose to the point of causing necrosis of the scrotum and yet could not sterilize the testis by a single

exposure. He then found that a smaller total dose divided in several exposures over 10 days was able to sterilize the testis without damage to the skin: this is what we call today fractionation [27]. Within the circumstances of his experiments, Regaud felt that the benefit was limited to 10 days. Henri Coutard (1876–1950), Regaud's associate, dared to extend the fractionation to several weeks of daily treatments and obtained unprecedented results in the treatment of cancer of the tonsil and larynx [3]. In the German literature this was referred to as 'Coutardsche Methode' or protracted fractional roentgentherapy [24].

Further progress came with the adoption of the roentgen (r), in Stockholm, in 1928; it resulted in better dosimetry and facilitated evaluation and comparison of results [10, 25].

In 1934, Irene Curie (1897–1956) and her husband, Frederic Joliot (1900–1958), working in the basement of the Radium Institute of Paris, discovered artificial radioactivity and opened the doors of nuclear medicine as well as of biologic tagging and of the industrial uses of radioactivity. From their work we have a host of radionuclides of common usage today [11, 21].

In 1942, Antoine Lacassagne (1884–1971) ingeniously showed that newborn mice put into anoxia survived doses of radiations that proved lethal to the nonanoxic control. Thus he showed the radiosensitizing role of oxygen [12]. Since then a succession of trials have taken place to seek an advantage in the radiotherapeutic margin of safety between destruction of the tumor and preservation of normal tissues [23].

In the 1930s, 'supervoltage' equipment of 700,000 V were produced in the United States and became available in very few centers. And in the 1940s, 'megavoltage' units of several million volts were produced. From then on the development of radiotherapy became accelerated and the milestones, being closer to us, are more difficult to discriminate.

This Symposium is dedicated to electrons and I should tell you something about electrons before closing. Sir Ernest Rutherford (1871–1937) called them beta-rays of radium. The early investigators of electromagnetic radiations observed the flying particles which Joseph John Thompson (1856–1940) called 'corpuscules' and were named electrons by Anton Hendrik Lorentz (1853–1923). In 1934, Brash and Lange [2], in Germany, were able to isolate electrons and produced epilation of the skin without apparent superficial effect. In 1940, Trump, Van De Graaff and Clorid [29], in Boston, were able to isolate what they called low intensity electrons; they demonstrated, by irradiating a pad of paper, that the top ones were not affected while the bottom ones were disintegrated. This naturally suggested that electrons could be used to irradiate tumors in depth without affecting the superficial tissues. In 1946, Kerst, Skaags, and

Lanzl isolated a beam of electrons [13]. Since then, Larry Lanzl and others have done considerable research which has brought them to your consideration.

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