Entering the Third Millennium After a Century of Ionizing Radiation in Science and Oncology

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Acta Oncologica Vol. 38, No. 7, pp. 819–821, 1999

Received 17 February 1999
Accepted 24 February 1999

It is just one hundred years since Marie Curie's discovery of natural radioactivity. This volume containing some invited papers from the 2nd Nordic Symposium on Radiation Oncology also marks that centenary. The last century has been remarkable in the inter-related fields of radiation science and cancer therapy. The discovery of both natural radioactivity and man-made radiation has transformed modern society in the field of medicine as well as in other areas. These discoveries are essential to our advanced technological environment and are used in many facets of ordinary modern life, such as for generating electricity, sterilizing foods, powering submarines, carbon dating and so on. They are also totally integrated into diagnostic and therapeutic medicine. The advent of radioactivity and radiation has transformed the fields of physiology and biochemistry, and our understanding of atomic physics and chemistry and molecular cell biology.

The obvious medical uses of x-radiography, e.g. for broken bones and chest ailments have been supplemented with radiological detection of malignancies, by external irradiation and by biochemical incorporation of tracer radionuclides. Advanced technologies that are now considered commonplace include scintillation counters, scanning and transmission electron microscopy, gamma cameras, computerized axial tomography (CAT) and position emission tomography (PET). These give another dimension to our understanding of structure and function in biology as well as better medical diagnoses. The new science of molecular biology and genetic engineering would not have been possible without recognition of the cell cycle, DNA damage, DNA repair enzymes and the use of radioactive nuclides as molecular tracers. Thus radiation science or its technological spin-off permeates the whole of modern science.

The possibility of using ionizing radiation for treating cancer was realized within the first year after Röntgen's discovery of x-rays. By the turn of the century, clinicians in several countries had found that tumours would regress if they were irradiated. It was soon recognized that the patients who could not be given the whole dose in a single session because they were treated on machines that sometimes broke down, and therefore received 'fractionated' radiation treatment, seemed to do better. Nowadays we recognize that the success of radiotherapy lies in the details of fractionation. Details of scheduling, especially fraction size, inter-fraction intervals and overall time are the key elements determining success and failure.

The early days of low-energy x-ray therapy with external beams gave way half a century later to the use of supervoltage photons. Then electrons, neutrons, π mesons, protons and heavy charged particles became available and have been considered for treating certain tumours. The two decades after World War II was a period when advances in the engineering areas of radiation sources had a huge impact. In addition to providing more penetrating beams of radiation to reach tumours at depth, these advances made the manufacture of radioactive isotopes possible. This replaced the extremely tedious and hazardous extraction of natural radio-isotopes that was the basis of Marie Curie's work. As a direct consequence, the early work with radium has been expanded by the availability of the other nuclides, many of them now man-made in nuclear reactors, in medical cyclotrons or other particle accelerators. Some of the most useful isotopes are so short lived that the patient must be at the site of nuclide production in order to use them for diagnostic procedures, e.g. studying metabolic defects or abnormal blood flow patterns.

One hundred years ago, the surgeon provided the only hope of cure for a cancer patient. Surgical treatment carried with it the certainty of significant mutilation, together with considerable loss of normal tissue form and function. The disease was often already well advanced and

 ISSN 0284-186X

distant metastatic spread had often occurred before the patient sought medical help. Diagnosis depended upon the patient recognizing the symptoms caused by a tumour and seeking medical advice. In those days the chances of treatment being curative were very poor. This was widely known and fear further discouraged the patient from seeking medical attention. Today, because of better diagnostic methods and because of better localization of the treatment, patients can be diagnosed and treated at an earlier stage in the evolution of their cancer. This has led to better treatments, less fear and now more than half of cancer patients are treated whilst the disease is still localized. Of course the chances of success in treating smaller and more localized disease are greater. Public awareness of this in the past few decades has reduced the fear of seeking medical advice and confirmation of the diagnosis. Thus many interdependent factors have led to a spiral of improvements.

Intra cavitary treatments for cervical cancer that were developed during Marie Curie's lifetime have been supplemented by the possibility of interstitial and even intracellular delivery of radioisotopes. Intracellular delivery uses characteristic biochemical or antigenic features of cells to target specifically to the tissues or cells of interest. These many advances in the potential applications of external beam and radio-nuclide irradiations have led to a remarkable increase in cure rates of many cancers, whilst conserving organ function and cosmetic appearance. Nowadays radiotherapy is as important a tool in the treatment of cancer as surgery. Indeed, when surgery, radiotherapy or a combination of the two is used, more than half of all localized cancers can be permanently eradicated with a minimum of disfigurement and with preservation of organ function.

Radiotherapy can now be combined with less extensive and less mutilating surgery. As the methods for defining the margins of a tumour improve, and computerized treatment planning systems become available, multiple external beams can be applied to deliver higher doses to the target volume and less to the adjacent critical organs. The aim is now conformal therapy with computerized optimization to produce the highest probability of tumour control with the lowest normal tissue dose volume histogram to minimize normal tissue toxicity.

Thus the past century has seen a transformation in the field of cancer therapy. Cancer no longer means a certain death sentence, although it is still a frightening word. In many western countries the 5-year survival rate from all cancers is approaching 60%, and even the 10-year survival rate is over 40%. A significant proportion of patients can have the disease completely eradicated, and return to the same probability of death from all diseases as the rest of the population, i.e. real cure. This is a revolutionary advance that has depended heavily on the tools provided by the discovery of ionizing radiation, both for the diagnostic and the therapeutic aspects.

The initial scientific advances that led to this impact on a lethal human disease were the discovery of x-rays by Röntgen in 1895 and of naturally occurring radioactivity by Curie and Becquerel in 1896. The Curie family in particular made a truly remarkable contribution. They showed the exceptional progress that can be achieved by a shared dedication to a common (scientific) aim. The work of Marie Curie and her husband led to the Nobel Prize in Physics in 1903 in recognition of the discovery and isolation of radium and polonium. A second prize awarded to Marie Curie in 1911 after her husband's tragic death, acknowledged her contributions to chemistry. Her daughter Irene, who had trained with her, went on to further discoveries with her own husband Frederic Joliot, which were recognized by a Nobel Prize in 1935, shortly after her mother's death. This illustrates the advantage that can come from a family partnership and must be balanced against the widespread fear of nepotism when relatives work together. There are many other examples of outstanding scientific marriage partnerships in cancer research and in radiation oncology, both within Sweden and across the world.

As the millennium approaches, there is increasing concern that women should be adequately recognized and represented in the academic sphere. Therefore it seems appropriate in this editorial to acknowledge several other major contributions from women scientists in the field of radiation science. Lise Meitner was one of the pioneers in atomic physics. Her experimental work in Berlin was essential to the model of atomic structure presented by Niels Bohr, which was recognized by a Nobel Prize to Bohr in 1922. Rosalind Franklin's experimental work in London on x-ray crystallography provided the images that led Watson & Crick to propose the 4-base alphabet in the complex language of the DNA double helix. Alma Howard's work with Stephen Pelc at Hammersmith Hospital, using radioactive tracers, provided the insight that DNA synthesis occurs in a distinct phase of the cell cycle. The definition of G1, S, G2 and mitosis forms the basis for all modern studies of growth control in molecular biology and biomedicine. Another remarkable insight using a radiobiological approach came from Tikvah Alper, also at Hammersmith Hospital. She first recognized, by UV absorption studies, that the slow 'viruses', which include scrapie and BSE, are not replicated or transmitted as nucleic acid, nor indeed as proteins. This provided the basis for another revolutionary discovery that led to a Nobel Prize, in this case to Stanley Prusiner. A common feature here is that all of these women have received very little public recognition.

The spin-off from radiation science to all branches of science, medicine and society at large has been enormous. The public perception of cancer as an inevitably lethal disease and of radiation only as a potentially lethal weapon is slowly changing. However, the facts show that over the past century the benefits of radiation have by far outweighed the harm. Many millions of cancer patients are currently still alive because of the dedication and resolve that has led to the refined use of radiation as a localized weapon in the fight against cancer. A knowledge of the exponential nature of cell kill and the causes of radioresistance makes it realistic to expect that the current cure rates will improve in the coming decades. A 10% increase in the dose to the target should result in a 20% or greater increase in local control rates on the steep portion of a dose-response curve. The difficult problem for the radiation oncologist is how to deliver that small increment in dose without exceeding normal tissue tolerance.

Success in treating localized tumours will extend to success in healing more advanced disseminated disease if the integration achieved so far between radiation physicists, radiobiologists and radiation oncologists is extended. We now need to find rational ways to include chemotherapy and other adjuvant therapies in an integrated and planned therapeutic strategy. A fully multidisciplinary approach to curative therapy should be the aim for the early decades of the next millennium.

The knowledge gained over the past century provides a good springboard for future advances. The challenge will lie in the increasingly difficult communication across diverse scientific frontiers and in careful translation of laboratory concepts into effective clinical implementation. At the 2nd Nordic Symposium in Radiation Oncology in Umeå in June 1998 a series of invited and proffered papers illustrated the extensive activity and the multidisciplinary nature of this field. The papers in this volume highlight some of the diverse aspects of cancer research in both the clinic and the laboratory that are the forefront of the field today.

During this conference, a day was dedicated to the 100th anniversary of the first publication on radioactivity from the very talented Curie family. Key topics were reviewed and the life and works of Marie Curie were presented, both from a Polish perspective and from a French viewpoint. Joseph Rotblat, who is also a Nobel Laureate and a Polish exile, had worked in the same laboratory as Marie Curie. He described his early work on the quantum theory of atomic structures, nuclear fission and the transmutation of elements. Through the Los Alamos project this led to the development of atomic bombs and the tragic experiences of Hiroshima and Nagasaki. Professor Rotblat recounted for the us the ethical and moral dilemmas of the Western scientists facing the possibility that the Nazis were on the verge of using the military potential of nuclear fission.

After the war Rotblat was appointed as a hospital physicist, working on the application of radiation for cancer treatment. His deep sense of moral responsibility also led him to give fifty years of effort with the Pugwash Committee, to control the danger to mankind that has resulted from the military application of basic radiation science. This effort has recently been recognized by the Nobel Peace Prize. It was interesting to hear that he and Marie Curie had both lived in the same street in Warsaw and worked in the same Institute. His presence at this meeting added a unique sense of historic continuity. His account illustrated clearly the broad spectrum of radiation science and both the potential dangers and the benefits.

We are grateful to the many sponsors who made the 2nd Nordic Symposium in Radiation Oncology possible, especially the Swedish Cancer Society, the Umeå University and our commercial colleagues. We appreciate this opportunity to share some of the highlights of the conference with a broader range of colleagues. This is possible because of the decision of the Acta Oncologica Board to mark the centenary of Marie Curie's work and to dedicate this issue of the Journal to the Proceedings of the 2nd NSRO Conference. The third meeting in this series will be held in Tampere, Finland, 22–24th November 1999. The fourth meeting is planned to take place in Denmark in 2001.