The History of Cancer Research: Introducing an AACR Centennial Series

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A century is only a small segment in the timeline measuring the history of science through the ages, but for cancer research, the last 100 years overshadow all of the years that came before. Physicians have moved from being able to do very little to treat patients to achieving survival and cure rates no one believed possible. Just a few decades ago, young investigators and physicians were often told not to go into oncology because the disease is so complex and the clinical outcomes were so discouraging. Today, oncology is one of the most exciting fields in biomedicine because of the many astonishing advances research continues to yield.

The field of cancer research had begun to grow rapidly by the end of the 19th century and the beginning of the 20th. In Europe, spontaneous tumors had been propagated in mice, and Gaylord and Tyzzer, two of the founders of the American Association for Cancer Research (AACR), soon expanded this research in America. Use of radium and X-rays was in its infancy. American institutes for research were being established (Roswell Park, The Rockefeller Institute, and The Institute of Cancer Research at Columbia University), and private endowments to fund research were beginning to proliferate, although direct government research support was not yet available. The first congresses on cancer had just been held in Europe.

The level of optimism was so high during this period that Roswell Park (who was instrumental in starting the institute at Buffalo now named after him) stated that the discovery of the cause of cancer was "just around the corner" (1). Within this spirit of enthusiasm, a group of 11 American pathologists, surgeons, and chemists proposed forming an organization. The AACR was founded in Washington DC on May 7, 1907, and its purpose was soon defined as "to further the investigation and spread the knowledge of cancer" (2).

It is interesting to reflect on what was known about cancer at the time AACR was founded (3). The earliest theory of cancer was based on the humoral theory of disease articulated by Hippocrates (460–370 BCE). It postulated that the disease was due to an excess of black bile. Apparently, this was not a bad hypothesis since it lasted about 1,900 years! However, during this time, the theory was never challenged by actual inquiry until the Renaissance, when anatomic dissection by Andreas Vesalius and others failed to reveal the existence of black bile. In the 1700s, it was postulated that cancer arose from coagulated lymph. The modern era of cancer research really began in the 19th century and led to the current concept developed by several investigators, notably Rudolf Virchow, that cancer is a disease of cells.

The first insights into human cancer causation occurred in the 18th century with the astute clinical observations by John Hill of the association of the use of snuff with nasal polyps, by Percival Pott of the association of soot with scrotal cancer in chimney sweeps, and by Bernadino Ramazzini of the association of reproductive factors with breast cancer. In the last decade of the 19th century, Ludwig Rehn reported an association between occupational exposure to aromatic amines and bladder cancer, thus setting the stage for the identification during the 20th century of other specific chemical carcinogens in the workplace and the environment.

Early evidence for the multistage and multifactor nature of the carcinogenic process was revealed by the experimental studies of Yamagiwa and Ichikawa at the beginning of the 20th century. Within just a few years after the founding of the AACR, the first tumor viruses were identified in chickens by Ellerman and Bong (1909) and Peyton Rous (1911). A few decades later, the Rous virus provided evidence for the first oncogene (src), and thus launched the field of molecular biology of cancer.

Tumor transplantation was reported by Mistislav Novinsky in 1877 and further studied by Carl Jensen in 1903. The technique of cell culture was established by Carrel and Burrows (1911). Gregor Mendel's Principles of Inheritance (1880) were rediscovered in 1900. The field of mouse genetics had just begun, with pioneering studies by Ernest Tyzzer (1908), as mentioned above, a founder of the AACR. Genetic studies in Drosophila had begun, and in 1914, Theodor Boveri made the prophetic postulate that chromosomes were the carriers of hereditary information and that cancer was due to defects in the chromosomes.

The exciting progress in cancer research during the past century has tended to parallel the successive developments in fundamental biology and biomedical research. Thus, in the late 1800s and early 1900s, the emphasis in cancer research was on cytology and genetics, and genetic studies in mice and humans continued to play a major role in cancer research. This was followed by studies in the field of biochemistry and intermediary metabolism (about 1920 to 1950), studies emphasizing DNA and nucleic acids (about 1950 to the present), studies on receptors and pathways of signal transduction (1980 to the present), and within the past decade, studies on gene transcription, epigenetic control of gene expression, genomics, and systems biology.

The very recent discovery, originally in plants, of the regulatory roles of small RNAs is also providing new insights into the biology of cancer. The latter example, which was totally unanticipated, suggests that within the next few years, other discoveries about fundamental aspects of cell biology will be made that will provide further insights into the wayward behavior of cancer cells. These successive themes have also influenced our understanding of cancer causation and provided new strategies for cancer prevention and treatment. Cancer researchers can take pride in the fact that cancer studies have often played an important role in advancing the broader fields of cell biology and biomedical research.

At AACR's first scientific meeting in 1907, in a small room in New York City, nine papers were presented. Two dealt with using transfusions to treat cancer; five covered transplantation of tumors

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in experimental animals; and two were meant to dispel the myth that some cancers were really infectious diseases (4). At the AACR's Centennial Celebration Annual Meeting in 2007 in a large convention center in Los Angeles, there were over 17,000 registrants, and over 6,500 abstracts and papers were presented, with topics ranging from antiangiogenesis to biomarkers, to epigenomics, to molecular targets, and to prevention and survivorship, terms not heard in cancer research in 1907.

The AACR is proud of the fact that our members have been responsible for so many scientific advances. Our meetings, conferences, task forces, and journals have provided, and continue to provide, the major forums for reporting, discussing, and disseminating cancer research, and AACR is playing an increasingly important role in research funding.

As part of our dedication to preserving the record of cancer research, and to celebrate our 100th Anniversary, the AACR has commissioned a series of historical review articles to be published serially in our flagship journal, *Cancer Research.* This history series is intended to cover the major scientific advances of the past 100 years in the fields of cancer causation, pathogenesis, prevention, and treatment. The articles are written by experts in the respective fields who are themselves responsible for some of the advances they will describe. The goal is not to produce a history of the AACR; this has been published elsewhere (1, 2, 5, 6). Rather, the group of articles will form a unique chronicle of progress, the factors that influenced the developments, their implications, and future directions in the field.

This issue of *Cancer Research* contains the first article in this series: "Advances in Chemical Carcinogenesis," by Loeb and Harris. It highlights the evidence that chemical agents play a major role in human cancer causation and the remarkable insights into the underlying mechanisms that have been obtained. The exciting advances in this field also have profound implications in terms of both cancer prevention and treatment.

Subsequent articles related to cancer causation will cover cancer epidemiology, tumor virology, and cancer genetics. Other articles will cover pathogenesis, treatment, and prevention. We thank the authors of these articles for their efforts and insights. We trust that readers of *Cancer Research* will find the articles not only of interest but also an inspiring record of scientific achievement.

Given how far our understanding of cancer at the clinical, tissue, cellular, and molecular levels has come in the past 100 years, it is not overly optimistic to think that well before the next AACR Centennial, the world will be celebrating a major reduction in cancer incidence and mortality. Exciting progress toward that goal is being made every day in our research laboratories and clinics.

Acknowledgments

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