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Editorial

The fruits of long endeavors – 200 years of oncology

It is said that if you know your enemies and know yourself, you will not be imperiled in a hundred battles; if you do not know your enemies but do know yourself, you will win one and lose one; if you do not know your enemies nor yourself, you will be imperiled in every single battle. – Sun Tzu

Hippocrates used the terms *carcinos* and *carcinoma* to describe non-ulcer forming and ulcer-forming tumors. Celsus (ca. 25 BC–50 AD) translated *carcinos* into the Latin *cancer*, also meaning crab.^{1,2}

We have come a long way from the times when cancer causation was believed to be due to imbalance of the four humors (body fluids). This belief held sway till buttressed by Galen.³ In 1761, Morgagni by doing autopsies to relate a patient's illness to post mortem pathologic findings laid the foundation for scientific oncology.^{2,3}

Rudolf Virchow, with the benefit of a microscope deduced the cellular origin of cancer in 1863. As Morgagni had linked autopsy findings seen with the unaided eye with the clinical course of illness, so did Virchow by correlating microscopic pathology to illness.⁴ Paget, in 1889 wisely mused about the seed-and-soil hypothesis of metastatic disease, a theory that is coming into its own today.⁵ The discovery of the structure of DNA by Watson and Crick in 1953 and eight years later, the genetic code broken by Nirenberg and colleagues, establishing the central dogma of biology; that information was transmitted from DNA to RNA and resulted in the synthesis of proteins.^{3,4}

The discovery of reverse transcriptase by Temin and Mizutani and Baltimore, which showed that information could be transmitted the other way, from RNA to DNA was a twist in the tale which had a profound influence on cancer medicine.^{2,4} In 1970, Smith and Wilcox identified enzymes that bacteria used defensively to cleave DNA at specific restriction sites.⁴ These discoveries gave birth to the molecular revolution and the biotechnology industry. They also paved the way for the sequencing of the genome. The increasing use of microarrays in cancer (first introduced in 2002) has revolutionized cancer diagnostics. The first cancer-directed microarray assay was approved by regulatory agencies in 2007 for breast cancer assessment⁶ and other applications are in the pipeline, including those for assessment of metastatic tumor

of unknown origin, leukemia, lymphoma, and colorectal cancer.

“On a new kind of rays”

In 1896 a German physics professor, Wilhelm Conrad Roentgen, presented a remarkable lecture titled “Concerning a New Kind of Ray”² which spread worldwide excitement. Within months, systems were being devised to use x-rays for diagnosis, and within 3 years, radiation was being used to treat cancer. In 1901 Roentgen received the first Nobel Prize awarded in physics.

The last hundred and twenty five years have shown astounding progress in cancer imaging and quantification leading to early diagnosis, detection of low volume residue translating into cures, reduced morbidity, mortality and better quality of life for cancer patients. Imaging currently is used for screening to detect cancer, characterizing lesions, performing loco regional and systemic staging, providing prognostic information, assessing response during and after therapy, restaging after treatment, performing follow-up of patients for recurrence, and precisely guiding therapies such as external beam radiation, brachytherapy, or thermal ablation.

The evolution of MR spectroscopy and diffusion MRI have shown great promise in understanding of tumor biology and tumor response assessment with considerable potential for response assessment in brain tumors and tumors in the bones. The fusion of anatomic and functional images to create hybrid “anatomomolecular images” with software or dedicated instruments such as PET/CT or SPECT/CT devices also is seeing rapid growth in applications in cancer imaging.

Physicians of Utmost Fame, Were called at once; but when they came, They answered as they took their Fees – “there is no cure for this Disease” – Hilaire Belloc

Our oldest description of cancer is found in Egypt and dates back to about 3000 BC. The Edwin Smith Papyrus is a copy of part of an ancient Egyptian textbook on trauma surgery.² It describes 8 cases of tumors or ulcers of the breast that were treated by cauterization with a tool called the fire drill. The writing says about the disease, “There is no treatment”. The

first abdominal surgery in the United States and proof that tumor masses could be cured by surgery came in 1809, when Ephraim McDowell removed an ovarian tumor without the use of anesthesia.⁴ Use of anesthesia by John Collins Warren 1864 and the introduction of antiseptics by Joseph Lister in 1867⁷ led to such an explosion in the field of cancer surgery that the next hundred years were rightly dubbed as “the century of the surgeons”.

Three surgeons stand out because of their contributions to the art and science of cancer surgery: Billroth in Germany, Handley in London, and Halsted in Baltimore. In 1894, when William Halsted⁸ introduced radical mastectomy for breast cancer his work was based in part on that of Handley, the London surgeon who believed that cancer spread outward by invasion from the original growth. At the same time Halsted and Handley were developing their radical operations, another surgeon was asking, “What is it that decides which organs shall suffer in a case of disseminated cancer?”. Stephen Paget, an English surgeon, concluded that cancer cells spread by way of the bloodstream to all organs in the body but were able to grow only in a few organs. In a brilliant leap of logic he drew an analogy between cancer metastasis and seeds that “are carried in all directions, but they can only live and grow if they fall on congenial soil”.²

In the first half of the 20th century, however, surgery was the only option, and a minority of patients could be cured by surgical removal of their tumors alone. Present day surgical oncology is based on the premise of “less is more”; the advances in imaging diagnostics, better equipment and technique have ensured minimal morbidity, mortality and ensured a better quality of life for the cancer patient.

We have found in (X Ray) a cure for the malady – Los Angeles Times, Apr 6, 1992

The discovery of radium by Pierre and Marie Curie in 1898 ushered in the era of radiation oncology. In 1928, it was shown that head and neck cancers could be cured by fractionated radiation treatments, a milestone in the field.² The modern era of radiation therapy began in 1950 with the introduction of cobalt teletherapy. Conformal radiation therapy (CRT), Intensity-modulated radiation therapy (IMRT), conformal proton beam radiation therapy stereotactic radiosurgery and stereotactic radiation therapy have evolved with advances in radiation physics and computing technology allowing the therapeutic radiologist to deliver beam energy precisely to the tumor and to spare the normal tissue in the path of the radiation beam.

Its palliation is a daily task, its cure a fervent hope. – William Castle 1950

Paul Ehrlich at the turn of the 20th century first made a concerted effort to develop chemicals to cure cancer. He coined the word “chemotherapy”.^{2,4} Two events provided optimism about the future of anticancer drugs: the use of nitrogen mustard in lymphomas at Yale in 1943 and Farber’s report in 1948 that folic acid antagonists could induce temporary remission in childhood leukemia.^{2,4} The evidence that childhood leukemia and advanced Hodgkin’s disease in adults

could be cured by combination chemotherapy in the 1960s⁹ provided the proof of principle, already established for surgery and radiation therapy, that drugs could cure any cancer.

Role of chemotherapy in adjuvant setting was heralded when two landmark studies of adjuvant chemotherapy in breast cancer were published: one which tested L-Phenyl Alanine Mustard and was reported by Fisher and colleagues in 1975,⁹ and one which tested a drug combination Cyclophosphamide, Methotrexate and 5-Fluorouracil reported by Bonadonna et al.¹⁰

The revolution in cancer research can be summed up in a single sentence: cancer is, in essence, a genetic disease – Bert Vogelstein

A major fillip in cancer management came in 2006 with discovery of Imatinib by Druker et al.^{4,11} in care of chronic myeloid leukemia wherein proof that treatment targeting specific molecular abnormalities that are unique to certain cancers could convert them into manageable chronic illnesses. Targeted therapy had come of age. Among the earliest targeted therapies that block growth signals introduced in clinical practice were trastuzumab, gefitinib, imatinib and cetuximab. The second-generation targeted therapies, like dasatinib and nilotinib produce faster and stronger responses and are much better tolerated.

The cancer therapeutic armamentarium has evolved with use of immunotherapy. Food and Drug Administration (FDA) approval of Rituximab for the treatment of B-cell lymphomas in 1997 and followed up by approval of Trastuzumab which paved the way for many other antibodies, most of which act by inhibiting growth factor receptors on the surface of cancer cells.^{2,4} In 2010, the FDA approved Sipuleucel-T (Provenge), a cancer vaccine for metastatic hormone refractory prostate cancer that boost the body’s immune response to cancer cells.⁴ The subsequent development of immunomodulatory agents such as ipilimumab, the development of cell-transfer therapies, and the use of genetically engineered lymphocytes to treat cancer have provided additional evidence of the ability of immunotherapy to mediate cancer regression.

This edition of the journal publishes three topics which encompass the entire gamut of oncology practice. PET/CT has revolutionized the imaging aspect of oncology with the availability of metabolic activity adding a new dimension to diagnostic and prognostication of disease.

Immunohistochemistry has become an integral part of diagnostic tools available to the onco pathologist for those morphologically challenging cases. Newer IHC markers are being discovered by the day which by improving diagnostic yield is translating into better patient care and clinical outcomes.

Rehabilitation and palliation are integral parts of oncological practice. Prosthetic and reconstructive surgery are the lynch pins which ensure that the cancer patient is accepted in his home, among friends on the job and by the society in general. Advances in prosthetics have gone pari passu with improvement in surgical oncological techniques and present day prosthetics mimic Gods’ creation as closely as it can. In the present century the growth in our knowledge of cancer biology has led to remarkable progress in cancer prevention,

early detection and treatment. We have learned more about cancer in the last two decades than had been learned in all the centuries preceding. More targeted therapies, nanotechnology, robotic surgery, expression profiling and proteomics are going to transform the oncological practice earlier and faster than we can imagine.

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