

EDITORIAL**A RADIATION BIOLOGIST LOOKS TO THE FUTURE**

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Once again we stand on a pinnacle of time. Backward we look to a year that has gone. Forward we look to the year ahead. Except that this particular pinnacle also separates the centuries and the millennia. Everyone, in every field, is taking stock: Where have we been and where are we going?

We celebrate 100 years of radiation research. As the nineteenth century became the twentieth, X-rays had already been discovered, X-rays were already being used for diagnosis, cancer patients were already being treated with radiation, and regrettably, we already knew that excessive doses of radiation could cause normal tissue damage and induce leukemia.

As this century comes to a close, and a new one begins, we have a fairly complete understanding of the effects of radiation at the cellular and tissue level and even at the level of the whole organism. This knowledge underpins the use of radiation as one of the most effective agents in the treatment of a wide range of human malignancies. The challenge now is to understand the biology of the cancer cell and to devise agents or strategies that exploit a differential effect on cancer cells based on the genetic defects they contain.

In the immediate postwar years, a clear view of the origin of cancer was lacking. We knew that cancers arise from cells that proliferate uncontrollably inside the body, and that this could be triggered by radiation chemicals and viruses, but the rest was a mystery. In a 20-year period from 1970 to 1990 the mystery of human cancer was in large part solved. We know that cancer is a disease of molecules and genes. Oncogenes came first as a great revelation in the early 1980s, though it soon became apparent that while activated oncogenes may be highly important in some leukemias and lymphomas, they were not associated with the bulk of human solid cancers. Deleted or inactivated tumor suppressor genes appear to be a more important cause of solid tumors, and while the principle was first demonstrated in cells cultured *in vitro*, it was the understanding of the role of suppressor genes in sporadic and familial retinoblastoma that opened up the field. The list of possible tumor genes grows daily, in parallel with the identification of genetic factors that make certain individuals, or groups of individuals, more susceptible to cancer.

This explosion of knowledge and understanding is very satisfying intellectually, but it has not (to date) done the patient with cancer much good! The vast majority of patients, when diagnosed with cancer, receive surgery and/or radiotherapy and/or chemotherapy just as they did 10, 20, or even 50 years ago! The new biology has yet to make an impact on cancer treatment, unless it is to make some people worry more because of the possibility that they are in a cancer-susceptible group with increased risk of multiple malignancies.

But this must surely change and change soon. This is the challenge of the new millennium. Just as trade followed the flag in colonial times, so treatment must eventually follow understanding. The parallel with bacteria and antibiotics is instructive. Pasteur identified bacteria as the cause of infections in the 1840s, but it was not until World War II, almost a hundred years later that antibiotics were developed. During that intervening century, physicians understood the cause of the infections that often killed their patients, but were powerless to do much about it, except treat the symptoms. The eradication of infectious diseases became a major step in human history with enormous sociological implications. We confidently expect that one day we will be able to treat cancer with agents that are specific for the cells that are malignant because of genetic defects. The eradication of cancer would be another major milestone in human history that would equal the victory over infectious diseases. As the century turns, no one can predict whether this will happen next year, or a hundred years from now. Likewise, no one can predict whether the cure for cancer will be the product of programmed and directed government-sponsored research or whether serendipity will rule the day as in the case of antibiotics, and so many other of the most significant steps forward in science.

Changes in treatment modalities, based on a knowledge of cancer genetics, must come and come quickly; first to augment and supplement existing methods and in the long run to replace them. So let's look into our crystal ball for a moment and try to predict some of the events as they are likely to transpire, recognizing that looking too far into the future is a hazardous business. No one in 1900, in their

wildest dreams, could possibly have imagined the changes and the progress that were destined to occur in the next century. As Yogi Berra put it so eloquently, "Predictions are difficult to make, especially about the future."

The first thing a radiation biologist should do while looking to the future is to check that his or her TIAA/CREF contributions are safely and wisely invested, because if events move as quickly as is possible, radiation biology could quickly join high-energy physics as a thing of the past. But this is unlikely in the short term and we will assume a more gradual rate of progress. The calendar may look something like this:

2010. By now 5 genes have been identified in the human population that give rise to increased radiosensitivity. Patients assigned to radiotherapy are routinely screened for these genes; the 5% or so who respond positively receive a reduced radiation dose or are considered for alternative therapy. The remaining 95% can receive an escalated dose with improved local control.

2015. Gene therapy strategies involving new suicide gene constructs are combined with radiation therapy for a variety of malignancies, including carcinoma of the prostate and breast cancer. The rationale is based on combining modalities that both target cancer cells, but have different normal tissue toxicities.

2020. New radioprotectors have been developed which can be delivered locally and topically, in order to protect normal tissues, such as the oral mucosa and salivary glands.

2025. Early diagnosis of radiation-induced second malignancies is now possible because of the identification of bloodborne proteins secreted by mutated genes.

2030. Tumor-specific antigens for all common human tumors have been identified, allowing early diagnosis from blood and tissue samples.

2035. Profiles of cancer susceptibility at a genetic level are now complete for the U.S. population. Targeted routine screening leads to early diagnosis. Individuals identified as susceptible to radiation-induced cancer may be directed to other forms of treatment.

2040. Radiation-directed gene therapy, as an adjunct to conventional radiotherapy, allows an improvement in therapeutic ratio. Promoters triggered by radiation confine the cytotoxic effect of suicide genes to the high dose target volume.

2050. Recombinant technology has improved to the point where proteins can be produced to make good the deficiencies resulting from inactivated suppressor genes in specific individual tumors.

2060. Protein peptide structures will be available to target specific DNA damage sites, in order to correct such defects.

2070. ASTRO Corporation dissolved following their 112th annual meeting at which radiation therapy was declared obsolete!

2095. On the two hundredth anniversary of Röntgen's discovery of X-rays a linear accelerator, complete with intensity modulation, was installed in the Smithsonian.