INTRODUCTION

The War on Cancer: An Update from the New Haven Theater of Operations

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In the early 1970s, the National Cancer Institute declared war on cancer. As in any military campaign, the first requirement for success is the accumulation of reliable intelligence about the enemy. The first few decades of this war were spent generating the tools to gather this intelligence: restriction endonucleases to analyze and restructure DNA and monoclonal antibodies to diagnose and treat cancer; recombinant DNA technology and the birth of the biotechnology industry; DNA sequencing techniques and the dawn of the genomics era; improved methods to analyze tumor cells; and better animal models of cancer. Armed with these tools, fundamental questions could be posed: What actually is cancer, what are its hallmarks, what are its causes, what are its vulnerabilities? The answers so far include the discovery of oncogenes and tumor suppressor genes, the elucidation of signaling pathways central to cancer development, the discovery that some human cancers are caused by viruses and bacteria, and the implementation of vaccination and antibiotic treatment strategies to prevent these cancers. Recent years also have seen the development of specific drugs that attack the molecular machinery of cancer, such as Herceptin for breast cancer and Gleevec for some forms of leukemia and other cancers. Indeed, for the first time, rates of cancer mortality in the United States are declining, largely due to improvements in our ability to diagnose and treat cancer in its earlier stages.

Despite these successes, cancer remains a formidable problem, and the public is impatient that progress has not been more rapid. There are several reasons why the war is not yet won. Cancer is largely a disease of aging, and the prevention of premature deaths caused by infectious diseases has resulted in the survival of more people into the years of peak cancer susceptibility. Other demographic factors, including the obesity epidemic and our inability to eliminate tobacco use, also hinder efforts to control cancer. The other major barrier to cancer eradication is its complexity. Cancer is not a single disease, but rather a collection of many different, albeit related, diseases. Although molecular studies have revealed that a relatively small number of biochemical and genetic pathways are responsible for cancer, the spectrum of cancers is quite diverse, depending on the specific cell types affected and the precise mechanism of carcinogenesis. Nevertheless, despite this complexity, a handful of general principles have emerged — cancer, even non-hereditary cancer, has largely a genetic basis; carcinogenesis is usually a stepwise process entailing the activation of cellular oncogenes and inactivation of tumor suppressor genes. The genesis of individual tumors can be pinpointed with precision from molecular characterization of tumor cells, information that
in some cases can provide important information about prognosis and treatment response. The pathways implicated in cancer often play crucial roles in the life and death of normal cells, the maintenance of genomic integrity, and organismal development. The immune system and other intrinsic defense mechanisms play a major role in preventing tumor formation.

We have made great headway in understanding cancer and are making the first inroads into targeted therapy, but much still remains to be done. This is an opportune time for a special cancer issue of the Yale Journal of Biology and Medicine. This issue contains articles, essays, reviews, case reports, and interviews that touch upon many important topics in contemporary cancer research, with a particular emphasis on work carried out at Yale.

A number of important themes are evident from the papers in this issue. First, together with focused studies of individual cancers, there is a need to consider broader paradigms of carcinogenesis. Two review articles address this issue. Is the standard multi-hit hypothesis of the sequential accumulation of mutations adequate to explain cancer, and is inflammation a common co-factor in cancer that needs to be explored more thoroughly? Second, as exemplified by a small series of case reports and articles, careful studies of tumors and patients can yield important information. Although much can be learned from cultured cells and model organisms, great insight also can be gleaned from studies of patients and patient material. This is especially true now that better tools are available to analyze and compare tumor and normal tissue. Such clinical studies are essential if cancer biology is to move beyond elegant mechanistic understanding to well-designed clinical trials and successful preventive measures and treatments. Third, studies on rare hereditary cancers can elucidate the fundamental causes of common, sporadic tumors.

Several articles imply that we are more similar to our cousins lower on the evolutionary tree than we might like to think, and great benefit can accrue from studies of organisms more amenable to detailed genetic studies because of their rapid generation time and simpler genetic and cellular make-up. Studies of yeast, roundworms, fruit flies, and mice all provide new insight into important topics such as the determinants of metastasis and the role of non-coding RNAs. Finally, a review article and an essay remind us that viruses are important human carcinogens uniquely susceptible to prevention through public health measures such as vaccination. In addition, studies of viruses have historically elucidated the basic molecular machinery of cell survival, growth, and cancer development, and viral-induced cancers may serve as useful model systems with well-defined targets to develop innovative treatment approaches.

Interviews with two Yale faculty members highlight the human dimension of cancer research. Both Haifan Lin and Tian Xu survived the excesses of the Cultural Revolution in China to establish outstanding research careers in the United States. Dr. Lin, the head of the new stem cell program at Yale, discusses the importance of cancer stem cells, a new concept that may deepen our understanding of the origins of cancer and improve our ability to treat it. He also considers the unique contribution that scientists at Yale, working with the support of the state of Connecticut, can make to studies in this field. Dr. Xu is pioneering innovative approaches to manipulate the mouse cell genome and study metastasis, the deadly process by which cancer cells spread throughout the body. He presents his vision for the future of cancer research and provides a glimpse of new technology that may revolutionize studies of cancer biology.

This is an exciting time in cancer research. We have seen many important discoveries, but it is clear much of the interesting biology that underlies cancer is still poorly understood. Attempts to transform our knowledge into more effective methods to prevent and treat cancer are still in their infancy. This issue of the Yale Journal of Biology and Medicine highlights some of the important advances that have occurred, frames some of the questions that remain, and provides insight into the approaches, ideas, and people who will carry the field forward.