CONCLUSIONS

The *War on Cancer* was given impetus by the *National Cancer Act of 1971*, which tapped the resources of the Federal government to confront the growing cancer challenge. As a result, all cancer initiatives funded by Federal dollars have been channeled through the NCI; itself remade by the National Cancer Act. While proponents who anticipated the conquest of cancer by the nation's bicentennial were overly optimistic and patently unrealistic, this book reviews the achievements and failures of the *War on Cancer* in an objective and dispassionate manner, based on factual data published in mainstream scientific journals and other reliable sources. Over four hundred pertinent, easily retrievable, and verifiable references are cited in support of the author's core argument that the *War on Cancer* was lost, and of his proposed three-layer approach to cancer control as an alternative to the failed cell-kill dogma that dominated clinical research and patient care for decades.

First, we must acknowledge that although the *National Cancer Act of 1971* has had a profound and multifaceted positive impact on basic cancer research, translational applications to patient care have lagged far behind. Indeed, while our knowledge in molecular biology and genetics of cancer has grown exponentially in the last 20 years, patient care has improved only marginally despite the cancer act. This is mainly due to undervaluing prevention and screening, and to our over reliance on inefficacious non-specific cancer drugs stumbled upon by serendipity or developed by a process of trial-and-error favored by the NCI, the main drug development funding source until recently. For example, molecular genetics is now poised to uncover the genetic defects underlying the emergence, growth, and dissemination of each of the more than 200 human cancers. In contrast, the 17 drugs recently identified by the World Health Organization as "*essential*" to manage cancer were developed between 1953 and 1983. Less than a handful of drugs developed since then is having a meaningful impact on cancer care. As a result, in 2003 fewer than 24,000 Americans with mostly advanced hematologic or embryonal cancers, representing approximately 2% of all cancers, were cured of their disease by chemotherapy used alone or in combination with surgery or radiation therapy. In contrast, over 550,000 Americans died of cancer that same year despite receiving a variety of cytotoxic drugs, often to the very end. Of these, over 150,000 or 28% of all cancer deaths died of tobacco-induced lung cancer, the most lethal though preventable malignancy in the US and worldwide, after an average survival of 7 to 8 months; a figure virtually unchanged since 1973. Thus, how are we to interpret reports of declining cancer incidence and death rates in the US after 1992 and of increased survival over decades? Is progress finally being made in cancer treatment? Unfortunately, the fall in incidence and mortality rates after 1992 did not extend beyond 1995 and 2000, respectively. Moreover, in 1997 fewer patients died of cancers with decreasing mortality rates (39% of total cancer deaths) than with increasing mortality rates (51% of total cancer deaths), and 86% of the decline was due to reduced death rates in only 5 cancers. Additionally, factors other than treatment have contributed to lower mortality rates after 1992, and to increased survival over several decades. While the latter is due mostly to improvements in overall health care over time, the former resulted from public education campaigns that foster prevention via reduction in environmental and behavioral risk exposure, and early stage diagnosis via screening programs. On the whole, fifty years of cytotoxic chemotherapy contributed minimally to the modest improvements in mortality rates or survival. This is because the faulty cell-kill paradigm, that views cancer as a "*new growth*" distinct from the host that must be eradicated at any cost, has misguided drug development and patient care for decades. From a treatment standpoint, surgery can satisfy this overriding principle because of its

ability to remove early-stage cancer visually discernible from neighboring normal tissues, but not current cancer drugs given their non-specific mechanism of action unrelated to the cancerous process. This, in large measure, explains why innumerable attempts to enhance the efficacy of cytotoxic drugs, mainly via drug combinations and dose escalation with or without bone marrow transplantation, have failed to substantially increase cure rates or prolong survival for most cancer patients.

That being the case, why does this failed system endure? The answer is multifaceted but can be summarized in one sentence. The information pipeline generated by clinical researchers and supported by their sponsors and publishers, fosters standards of care that are reinforced by financial incentives and the extraordinary capacity of physicians for self-delusion, and by unrealistic expectations of consumers nurtured by the media. Thus, the time has come to abandon the cell-kill paradigm and to anchor cancer control on an incremental, three-tier approach that incorporates prevention, early diagnosis, and when these fail, on controlling the aberrant genetic defects that lead to the development, growth, and dissemination of cancer. Is this approach likely to succeed where the cell-kill paradigm failed? It could be argued that, tough flawed in retrospect, past cancer control strategies seemed sound when first proposed and that the new paradigm might also lead us astray. However, in contrast to hypothesis-driven past strategies the present proposal is solidly anchored on proof of concept for each of its components. Prevention has been confirmed by the success of anti-smoking campaigns in reducing the incidence of lung cancer in American males and by hepatitis B immunization programs in reducing the incidence of liver cancer in Taiwan. Screening programs to uncover cervical, prostate, and breast cancer in surgically-curable early stages are saving lives, though screening tools at our disposable today are insensitive and confined to only a few cancers. Finally, the feasibility of controlling aberrant genetic defects underlying cancer rather than killing the affected cells has been amply demonstrated by the efficacy of Imatinib mesylate, the first specific, molecularly-targeted anti-cancer agent of the post-genomic era. Ultimately, the success of the proposed measures will require a strategic shift from reliance on the conceptually faulty and operationally failed cell-kill notion of cancer treatment to a post-genomic cancer control paradigm. The new paradigm calls upon policy makers to enact enlightened public policies designed to develop and implement cancer prevention and screening programs of national scope and achievable goals. It also calls upon medical researchers to develop simple, specific, and cost-effective screening tools for the early detection of all cancers, and to exploit the vast genomic database towards translational therapies for patients with advanced or progressive malignancies. At the community level, it urges practitioners to focus on patient rather than tumor-outcomes, and to ensure that potential risks are justified by expected benefits.