Review article

The war on cancer

Michael B Sporn

25 years ago, then President Nixon "declared" War on Cancer. In this personal commentary, the war is reviewed. There have been obvious triumphs, for instance in cure of acute lymphocytic leukaemia and other childhood cancers, Hodgkin's disease, and testicular cancer. However, substantial advances in molecular oncology have yet to impinge on mortality statistics. Too many adults still die from common epithelial cancers. Failure to appreciate that local invasion and distant metastasis rather then cell proliferation itself are lethal, obsession with cure of advanced disease rather than prevention of early disease, and neglect of the need to arrest preneoplastic lesions may all have served to make victory elusive.

Dead, your majesty. Dead, my lords and gentlemen. Dead, Right Reverends, and Wrong Reverends of every order. Dead, men and women, born with Heavenly compassion in your hearts. And dying thus around us every day.

—Charles Dickens, Bleak House, 1852–53

This magnificent quotation provides a unique summary on the total success of the "War on Cancer" during the past 25 years. The "campaign" began in 1971 when then President Nixon declared war against cancer, a move that led to the National Cancer Act (1971). Although immense advances have been made in basic scientific knowledge and in clinical treatment and cure of certain malignancies, especially the leukaemias and lymphomas, the fact remains that the goal of substantial reduction in overall death rates for most of the common carcinomas, which account for most cancer deaths, has not been met (figure 1).[1,2] 10 years ago, in a prominent review that was highly critical of the emphasis on treatment of cancer as opposed to prevention,[3] it was predicted that the National Cancer Institute (NCI) would not achieve its stated target of a 50% reduction in cancer mortality by the year 2000. Indeed, recent analyses from the NCI indicate that overall mortality from cancer in the USA actually rose from 1973 to 1992.[1,2] Although there have been slight declines in rate of mortality from breast and other cancers in America, Europe, and Japan,[4,5] the magnitude of these declines hardly justifies any optimism that we have won a war.

Too many men and women are still dying from carcinomas of the lung, breast, prostate, ovary, pancreas, and other epithelial tissues. Thus for many of these conditions, the prognosis for the patient who is diagnosed with advanced invasive and metastatic disease remains little better than it was 25 years ago. As we approach a 25th year of this immense war to find a cure for cancer, we need to re-evaluate our triumphs and failures, and ask "Why have we succeeded so brilliantly with treatment of acute lymphocytic leukaemia in children, yet failed so dismally with treatment of advanced lung, pancreatic, or ovarian carcinoma?" I start with the assumption, perhaps a prejudice, that cancer is a preventable rather than a treatable disease, and that much of our frustration with the "cancer problem" stems from our inability to bring this concept to fruition.

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Triumphs

There have been so many major triumphs during the past 25 years that it is impossible to mention them all. The successes in the use of chemotherapy and radiation (as documented in many textbooks) to provide cures for acute lymphocytic leukaemia and other childhood cancers, Hodgkin's disease, and testicular cancer, as well as the development of early detection and adjuvant therapy for breast, colon, ovarian, bladder, and cervical cancer are among the great achievements of modern medicine. The heightened interest in the cancer problem achieved by increased funding and dissemination of information has revolutionised the approach to the disease, from increased public awareness to better surgical treatment and more humane management of terminal illness.

Cancer is out of the closet, and community and patient involvement is a force that drives efforts at better and earlier diagnosis, more sparing approaches to surgery,

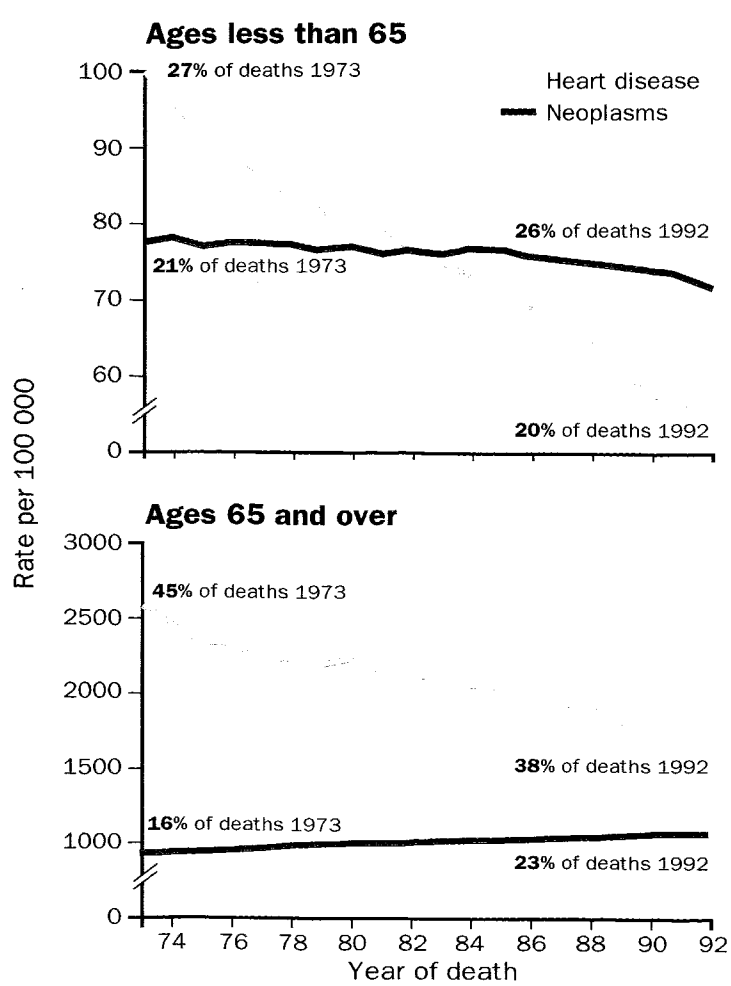

Figure 1: **Mortality from cancer and heart disease in the USA, 1973–92**[2]

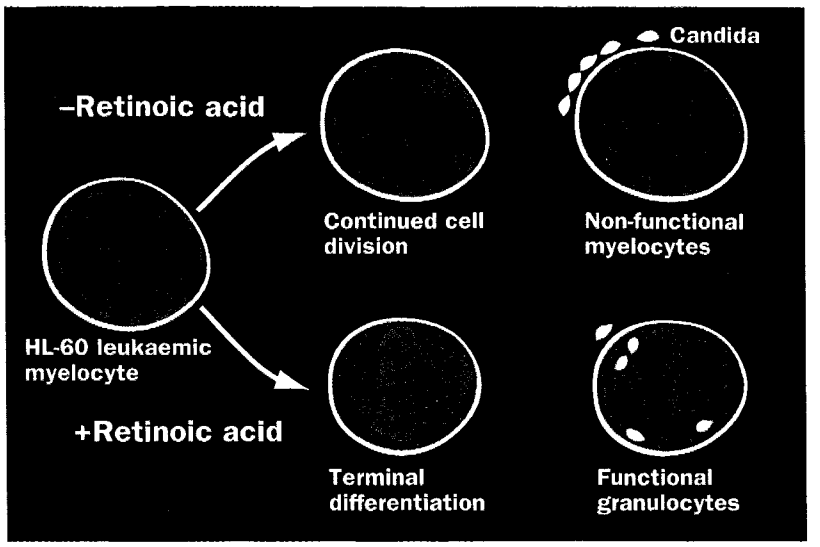

Figure 2: **Induction of normal differentiation by all-trans-retinoic acid in human leukaemia cells**[15]

heightened efforts at prevention, as well as increased levels of basic research. Epidemiology has played a tremendous role in saving lives with the recognition and acceptance of tobacco as a major aetiological factor in human cancer. Better diagnostic techniques are now available (cytological and imaging) for detection and eradication of early lesions although, as I will discuss later, early diagnosis is often late diagnosis. The surgical approach to the patient has changed dramatically, with the development of new procedures that allow less radical surgery of the breast, and sparing of limbs, larynx, and the need for ostomy. More radical procedures for prostatic and liver surgery have saved lives of patients with advanced disease. Supportive care for patients has been revolutionised with the introduction of new devices, pumps, appliances, and drugs such as anti-emetics, which enable a patient to continue a relatively normal life while undergoing treatment. For those who do not respond to treatment, the hospice movement and the liberal use of narcotics during terminal illness have greatly eased the pain of dying.

Perhaps the greatest advance of all, which has yet to influence the mortality statistics, is the explosion in basic scientific knowledge about cancer. The revolution in basic molecular and cell biology, fueled in large part by the emphasis provided by the War on Cancer, has led to awesome new discoveries relating to individual oncogenes, tumour suppressor genes, peptide growth factors (cytokines), and regulation of gene expression and cell function.[6–9] The discovery of the steroid receptor superfamily and its central role in cell differentiation and homoeostasis has provided a major unifying theme.[10] The power of genetics, not only in mammalian organisms but also in invertebrates such as drosophila and *Caenorhabditis elegans*, as well as yeast, as a tool for analysis becomes increasingly important. The intellectual brilliance of the new molecular biology and its power for development of new diagnostic and therapeutic modalities are immense.

At the same time, cell biology studies have shown that certain malignant cells can sometimes be induced to differentiate into normal cells without killing them. Based on pioneering studies in teratocarcinomas,[11,12] it was shown that malignancy could be reversed in murine[13,14] and human[15] leukaemia cells without killing them (figure 2). These studies have revolutionised thinking about cancer and have led to successful treatment of human disease.[16] Whilst reductionistic science has been triumphant in this area, major gaps in knowledge remain, relating to the integration of all the individual pieces into a coherent biological framework. Carcinoma is a disease of the whole organism. Although molecular and cell biology have immense power as analytical tools, the ultimate understanding and control of the process of carcinogenesis will require a new synthesis at the levels of tissue, organ, and organism.

Why no decline in overall mortality?

If we have accumulated so much basic knowledge about the molecular biology of cancer and if we have been so successful in curing some cancers, especially in younger patients, why have the overall mortality figures not diminished significantly? The proposition that if we subtracted the data from the lung cancer epidemic from the statistics things would look much better is only half-true: there are still far too many deaths from carcinoma of the breast, prostate, ovary, pancreas, colon, and other common epithelial sites. Perhaps some of our underlying assumptions about cancer and our approaches at control have been incorrect.

I suggest three areas in which this is the case. First, we have not had a realistic understanding of the natural history of the genesis of invasive and metastatic carcinoma. It is local invasion and distant metastasis that kill rather than excessive cell proliferation per se. Second, there has been an obsession with the concept of "cure" of advanced disease, as opposed to prevention of early disease; this is particularly true of many well-intentioned philanthropic efforts. Third, there has been inadequate effort devoted to the pharmacology of arrest of preneoplastic states and prevention of invasive and metastatic disease. The cardiovascular research community, by contrast, has been uniquely successful in establishing significant biomarkers to direct the development of a large pharmacopoeia of chemo-preventive agents, which have contributed significantly to the decline in cardiovascular death rates (figure 1). In each of these three areas, there are questionable assumptions that have been made by both basic scientists and clinicians, particularly with respect to epithelial carcinoma.

Natural history of carcinogenesis

As I have noted, the disease is not cancer but the process of carcinogenesis, which often has a 20 year (or more) latent period before invasion and metastasis occur.[17–19] Above all, invasive epithelial carcinomas are not the primary and exclusive result of excessive cell

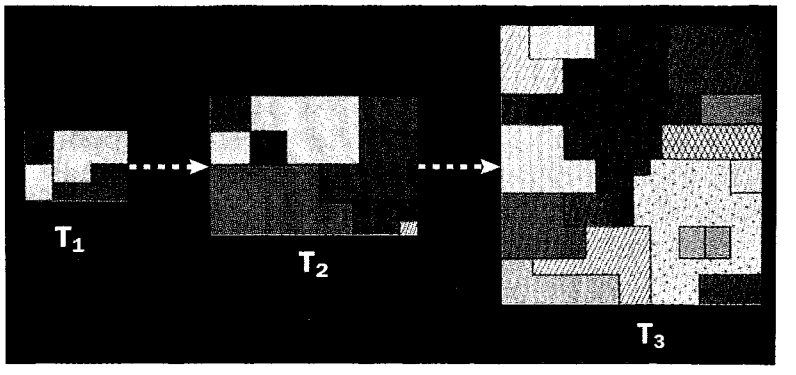

Figure 3: **Diagramatic representation of increasing genetic and phenotypic diversity of carcinomas during tumour progression with increasing time (T_1, T_2, T_3)**
See ref 27. Reproduced by courtesy of G Poste.

proliferation.[20] This is a widely held misconception, for it is well known that many normal tissues proliferate much more rapidly than cancerous ones. Carcinoma does not arise when a single cell changes ("transforms") so that it divides continuously, which is another common misconception. Rather, the process of carcinogenesis, which is driven by multiple interactive factors, including genetic mutation, excessive cell proliferation, and changes in the extracellular milieu, entails a prolonged series of many failures in the reciprocal interactions between epithelium and its underlying stroma.[21-23] These interactions are critical for the regulation of normal cell differentiation.

Carcinoma is ultimately an aberrancy in normal cell differentiation and survival,[11,12,24] not a disease intrinsically caused by excessive cell proliferation. During embryogenesis, the under-lying stroma (mesenchyme) is a critical determinant of the organ-specific differentiation of overlying epithelium in particular tissues. Epithelium and its stroma are in constant reciprocal communication with each other throughout life, and cancer is the end-result of a defect in this communication, which is required to maintain normal differentiation.[23] Reductionistic molecular theories of cancer causation that focus on epithelium alone cannot be completely adequate, since they ignore a vital part of the intrinsic biology of carcinogenesis.[6,7] There is a critical need for further studies on the role of stroma as a determinant of carcinogenesis, as seen in the recent emphasis on the importance of angiogenesis (blood vessels are derived from mesenchyme) for both carcinogenesis and metastasis.[25] Furthermore, simplistic notions of transformation and excessive cell proliferation also ignore the problem of tumour cell heterogeneity,[26,27] which has been a major obstacle to successful chemotherapy of advanced tumours. As carcinomas progress they became increasingly heterogeneous (figure 3). The cells in advanced metastatic carcinomas may have numerous genetic abnormalities, and these abnormalities may vary from one cell to the next within the carcinoma, as a result of the aneuploid nature of lesions. Thoughts of gene therapy directed at single oncogenes or tumour suppressor genes in such a context seem hopelessly naive.

In the analysis just presented, I emphasise that carcinoma and leukaemia are undoubtedly very different diseases, both in pathogenesis and response to treatment. This is particularly true for those leukaemias with few genetic lesions; these conditions tend to respond well to cytotoxic therapy, while advanced carcinomas, which are karyotypically more complex[28,29] as well as other leukaemias which also have more genetic diversity, have been a difficult target for the therapist.[30] Leukaemia is a poor model for the understanding of carcinoma.

Figure 4: **Hercules and the Hydra, a nine-headed monster**
One of the labours of Hercules was to kill the Hydra. One head was immortal, and when each of the others was severed, two new ones replaced it. Illustration by Giovani Caselli, in *Gods, men, and monsters from the Greek myths*, by Michael Gibson. Reprinted with permission from the publisher Eurobook Limited.

Emphasis on cure

Everywhere, one sees emphasis on the "cure for cancer", especially in the public hype that has been generated by the War on Cancer. The attempts to cure advanced disease are frustrated by the extent and heterogeneity of the tumour burden and the acquisition of multiple drug resistance and survival mechanisms in the diverse population of cells that comprise advanced lesions. Given the genotypic and phenotypic heterogeneity of advanced lesions, it becomes difficult to know exactly what we wish to cure. A lesion that appears to be anatomically defined may in reality be multiple lesions, each with its own phenotype. The Greek metaphor of the multiheaded hydra is most germane (figure 4). The misperception of cancer as a fundamentally proliferative disease has led to an overemphasis on development of cytotoxic drugs that kill cancer cells but which unfortunately are also toxic to many normal tissues. Although normal bone marrow can be protected from cytotoxic agents by its autologous transplantation or the use of haemopoietic cytokines, the heart, lungs, kidney, brain, and gastrointestinal tract may all be severely damaged by the use of dose intensification.[31] Furthermore, such dose intensification often leads to emergence of new clones of drug-resistant cells or new cancers in other tissues,[32,33] particularly because cytotoxic agents themselves are often mutagenic. Common sense says that it would seem more prudent to consider the use of drugs to arrest or prevent carcinogenesis during its early stages, when a lower level of genetic damage may still allow preneoplastic cells to differentiate into more normal cells, and when one can realistically use agents that are essentially non-cytotoxic and non-mutagenic.

Chemoprevention of carcinogenesis

The exciting and important advances that have been made in the genetic diagnosis of risk factors now bring the subject of chemoprevention of cancer to the forefront. If a young woman is born into a family with a high risk for breast cancer, and she is found to have a mutation in the *BRCA1* gene, what are we to do?[34,35] Watchful waiting with attendant anxiety, prophylactic mastectomy, frequent mammograms, or something else? It is remarkable that so little has been done to couple chemopreventive strategies with genetic diagnosis. Chemopreventive agents may be used in two ways: to prevent further DNA damage that would enhance carcinogenesis, or to suppress the appearance of the invasive or metastatic phenotype, in the face of known mutation.[24,36-38] The natural history of carcinogenesis tells us that most preneoplastic lesions do not progress to fully invasive cancer, because epithelia, in cooperation with their underlying stroma, have mechanisms to suppress carcinogenesis.[18]

Many new drugs are highly active in experimental systems in enhancing such suppressive mechanisms. The retinoids and the oestrogen-response modifiers are examples of agents that can prevent human cancer, without extensive toxicities.[38–43] The concept of using either retinoids or tamoxifen to suppress carcinogenesis has existed for over 20 years, but there is still great opposition to the use of these substances in a clinical prevention setting. This attitude is based on the fallacy that patients are still "healthy" while they have preneoplastic lesions, and that it is not ethical to start treatment until invasive disease occurs.[18] Such opinions fortunately have not prevailed in cardiovascular medicine, and there is accepted and widespread use of chemopreventive agents to lower serum cholesterol or blood pressure before patients develop the serious arterial lesions that are the vascular counterpart of in-situ carcinoma.[44–46]

We should ask why the oncology community and the public at large have been so resistant to this chemopreventive approach to cancer, when it has played such an important role in lowering cardiovascular mortality. Concern about potential side-effects of chemopreventive agents (and even possible legal liability as a result) has been a major deterrent to more widespread use of chemoprevention. We need to develop some form of insurance to compensate the very small number of people who might have an idiosyncratic or undesirable reaction to a preventive agent, while a large number of people benefit greatly from its administration. Society already insures for many such risks of beneficial agents and technology, and this concept needs to be extended to clinical chemoprevention of cancer.

It will be important to find new agents that are even safer than the presently available ones, and also to consider concomitant use of multiple chemopreventive agents ("combination chemoprevention").[47] Clinical chemoprevention is still in its infancy, with its unique set of problems and need for further support.[36] Unfortunately, a disproportionately low level of funding, both within the academic research establishment as well as in the pharmaceutical industry, is still being given to chemoprevention research, as opposed to efforts directed toward the treatment of cancer. Furthermore, we need to bolster educational efforts to encourage changes in lifestyle, diet, and other natural factors that might suppress the process of carcinogenesis.

Conclusion

There have been major triumphs, clinical and scientific, during the past 25 years of the War on Cancer. However, common carcinomas continue to be a major cause of death and suffering, particularly in adults. We must develop new approaches to control this plague of deaths, adopting an ethic of prevention,[48] based on a more sophisticated understanding of the process of carcinogenesis and the potential to prevent disease before it becomes invasive and metastatic. Reductionistic molecular biology can only proceed so far with its brilliant analysis of all the bits and pieces that comprise the organism. Carcinoma is not a disease of an individual cell. Carcinoma is ultimately a more complex failure in homoeostasis, a chronic, maladaptive tissue and organismic response to injury.[22] Carcinogenesis is a contextual process in which epithelium and mesenchyme fail to communicate properly with each other, resulting eventually in invasion and metastasis.[23]

It has taken millions of years of evolution to organise groups of cells as functional tissues. When driven by mutagenesis, this organisation unravels, resulting in carcinogenesis, and eventually leading within 20–30 years to the chaos that is cancer. We have a unique opportunity to suppress the chaos, since the unraveling process is prolonged and manifests in preneoplastic lesions detectable with biological and molecular markers during early carcinogenesis. Cells and tissues have intrinsic capacity to control or reverse this entropic degeneration; we know that many preneoplastic lesions disappear spontaneously without pharmacological intervention.[18]

It would therefore make sense to enhance these physiological homoeostatic processes to control carcinogenesis and prevent endstage disease. We need more intensive efforts to prevent damage to DNA, whether it be by blocking tobacco addiction in teenagers or blocking chemical activation of carcinogens by P-450 enzymes. We need to develop a new basic and clinical pharmacology of chemopreventive agents to suppress tumour promotion and progression, and to offer real hope for those at genetic risk for disease. Just as smallpox and poliomyelitis deaths have been eliminated and cardiovascular deaths have been greatly curtailed by preventive approaches during the past 25 years, we should hope that the next 25 years will see the emergence of a truly preventive approach to cancer. Meanwhile the triumphs that we have seen during the past 25 years in treatment, with chemotherapy, radiation, and surgery, need to be extended to provide a last resort for the patients whose disease is not arrested by prevention.

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