# A Review: The War on Cancer

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***Abstract-*** *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.*

## I. 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.

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.

## II. 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 halftrue 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 chemopreventive agents, which have contributed significantly to the decline in cardiovascular death rates 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.

## III. 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. B7-19 Above all, invasive epithelial carcinomas are not the primary and exclusive result of excessive cell proliferation (21), 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.

## IV. 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. 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 (3)' Furthermore, such dose intensification often leads to emersence 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.

## V. 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 BRCA 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)

## VI. 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 (2) 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)

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