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Perspectives in Cancer Research

Carcinogenesis and Cancer: Different Perspectives on the Same Disease[1]

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> All I maintain is that on this earth there are pestilences and there are victims, and it's up to us, so far as possible, not to join forces with the pestilences. That may sound simple to the point of childishness; I can't judge if it's simple, but I know it's true. You see, I'd heard such quantities of arguments, which very nearly turned my head, and turned other people's heads enough to make them approve of murder; and I'd come to realize that all our troubles spring from our failure to use plain, clean-cut language.
>
> *The Plague*
> Albert Camus

This brief perspective is based on the Bruce Cain Memorial Lecture presented at the 1991 Annual Meeting of the American Association for Cancer Research. The problem it considers can be simply stated: cancer is an endemic pestilence, and we are the victims of our own failure to use plain, clean-cut language to describe its very nature. In spite of the striking advances that have been made in the treatment of leukemias, lymphomas, and related diseases, the prognosis for the patient with the most common types of invasive, metastatic carcinoma, such as those originating in epithelia of the lung, colon, pancreas, breast, oropharynx, bladder, or prostate remains very bad indeed (1). This situation is a consequence of our misperception of the pervasive, endemic nature of cancer and our historical failure to use proper language to describe its pathogenesis. The failure to use appropriate terminology to define the nature of cancer in turn has perpetuated this widespread misperception of the intrinsic endemic nature of the disease, resulting in inadequate approaches to its control.

The Need for a New Definition of Cancer

The very name, "cancer," (a term widely used by clinicians, laboratory scientists, and laypersons alike to describe the plague that is upon us), is indeed a misnomer. The disease in reality is a process, namely "carcinogenesis," rather than a state, as implied by the term, "cancer." As we have noted elsewhere (2), the actual disease is an evolving molecular and cellular process, not a static circumstance, the onset of which can be dated to the time when a pathologist can finally see cells invading through a basement membrane on a slide. Classical terminology, which originated more than a century ago, ignores the importance of the critical dimension of time in the development of epithelial carcinogenesis; by now, we know that there is a latency period, often 20 years or more, between the initiation of carcinogenesis and the onset of the terminal, invasive, and metastatic phase of the disease. Classical pathology and clinical oncology have dealt with cancer in the three dimensions of space (the size and location of lesions); to understand the process of carcinogenesis, which is the reality of the disease, we must now add the dimension of time.

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A more realistic and modern view would be to consider the process of carcinogenesis as a 4-dimensional process of dysregulation of gene function (whether caused by mutation, deletion, amplification, translocation, or some other mechanism), leading first to clonal expansion and clonal heterogeneity of initiated and promoted cells, second to local tissue invasion, and finally to metastasis. At the present rate of discovery of oncogenes and suppressor genes (3, 4), it is conceivable that hundreds of genes will eventually be implicated in the process of dysregulation that finally leads to the invasive or metastatic phenotype; in any individual patient with metastatic carcinoma this is manifested by a wide array of genotypes and phenotypes within the population of tumor cells in that patient (5–7).

We thus need to develop a kinetic perspective of the entire process of carcinogenesis, particularly the kinetics of the development of the early lesions of the disease. We must emphasize that there is only a stochastic probability that an early stage will progress to a later one. Indeed, the natural history of many forms of epithelial carcinogenesis indicates that many, if not most, early lesions disappear spontaneously (8). Because these early lesions often disappear, it has been erroneously concluded in the past that they are not relevant to cancer. Indeed, it is widely believed by many physicians that the patient with such an early, noninvasive lesion "does not have cancer." This is clearly a fallacious interpretation. To the extent that everyone is subject to mutation, either endogenous or exogenous, everyone is part of the carcinogenic process. Given the ubiquitous nature of both natural and man-made carcinogenic substances in our environment, it is doubtful whether the genome of any adult man or woman has sustained no damage over the course of that individual's lifetime. Thus, carcinogenesis is an endemic disease process, and essentially no one is entirely healthy from a genomic perspective. Everyone is at risk, and indeed, although progression from early to late lesions may be stochastic, at the present time an epidemiologist can accurately predict that about 1 in 5 persons in the entire population of the United States will eventually die of end-stage malignancy if the current death rates continue (1).

There are several other logical fallacies that have resulted from the failure to use plain, clean-cut language to describe the process of carcinogenesis. The worst fallacy is the widespread notion that people are "healthy" until they have "cancer," as if one could set a date upon which the cancer began. The date that a woman can first feel a lump in her breast or that this lump can be detected on a mammogram is totally irrelevant to the understanding of the pathogenesis of invasive breast cancer. Carcinogenesis begins with the earliest damage to any regulatory gene that is relevant to the disease process, even though it may be many years before the phenotypic manifestations of this damage are apparent. Corollary fallacies are the notions that it is unethical to treat "healthy" people with a preventive agent and that one must wait until a diagnosis of "cancer" is made on a patient before it is ethically justified to treat that patient with a "cancer drug." Perhaps the best way to expose such reasoning as fallacious is to examine the progress that modern

medicine has made in the conquest of another pestilence, namely syphilis.

There are many analogies that can be made between the natural history of cancer and the natural history of syphilis. Both diseases have an initiation phase which causes little biological morbidity to the host, and death ensues in a relatively small fraction of the original population at risk only after a long latency period. In syphilis, as in epithelial carcinogenesis, this latency period may be 20 years or more. In both diseases, a progressive evolution of several stages occurs, and in neither disease is this progression inevitable (8, 9). Indeed, the majority of people who have been initiated in either disease process will *not* progress to the final lethal stage, even without treatment. The statistics for untreated syphilis have been particularly well documented, especially in the famous study conducted many years ago in Oslo, Norway (10). Thus, less than one-third of the Norwegian cohort with the primary lesion of syphilis (the chancre), when left untreated, eventually developed late destructive lesions, such as those of the cardiovascular and central nervous systems, which cause death. Most notably, two-thirds of the total, untreated ("initiated") individuals went through life with minimal or no physical inconvenience.

Fortunately, in its successful control of the plague of syphilis, modern medicine did not adopt the same fallacious terminology that still pervades the field of oncology. In spite of the fact that two-thirds of the patient population with primary lesions of syphilis can go through life with essentially no ill effects if left untreated, it was realized that a common disease process pertained to the entire patient population with such early lesions, even if there was only a stochastic probability of progression to a more serious stage. Thus, it is now considered appropriate, ethical, even necessary, to treat all patients with early syphilitic lesions with chemotherapy, even though the majority of these patients could go through life with no treatment and suffer essentially no ill effects. The eradication of syphilis as a fatal disease, by virtue of recognizing the importance and significance of early lesions in its pathogenesis, has been one of the great triumphs of modern medicine.

In contrast, in oncology, most clinicians and pathologists refuse to recognize that early lesions have any biological significance, and indeed very little effort is devoted in cancer research to the study and control of such lesions. We reserve the term, "cancer," for late lesions; one might contemplate what the consequences might have been if the term, "syphilis," had been reserved for tertiary lesions of that disease and the chancre had been considered to be a somewhat irrelevant precursor of the true disease. One might wish to examine why there has been such a difference in approach to the two disease processes. In the case of syphilis, successful therapy has been available to eradicate or control early lesions, whereas it has been extremely difficult to influence the progression of the early lesions of carcinogenesis. Moreover, the endemic nature of the problem of carcinogenesis has made it extremely difficult for physicians and laypersons alike to accept the notion that we all have precursor lesions for what may develop into lethal disease. Furthermore, the probability that lesions will progress is undoubtedly less in the case of carcinogenesis (unless one is considering relatively rare syndromes, such as familial polyposis), as compared to syphilis. The existential perspective that "each of us has the plague within him; no one, no one on earth is free from it (11)" is not particularly agreeable to most people. If some effective and acceptable method for treatment of carcinogenic precursor lesions were available, there would be greater acceptance of their relevance. Meanwhile, since such lesions cannot be effectively controlled, they are largely ignored.

Prevention of Carcinogenesis

Once one accepts the concept that carcinogenesis is an endemic process that affects essentially everyone, then the need to develop some practical approach to prevent it becomes self-evident. It should be apparent, from a pragmatic viewpoint, that to sit back, passively do nothing, and watch the evolution of early lesions of carcinogenesis until they become invasive is in itself an active decision. As noted above, this strategy has not been very impressive in improving the prognosis of the patient with invasive carcinoma. Both logic and common sense indicate that it would make sense to try to find some active intervention to prevent progression of early lesions. The difficult question has been how to do this.

Equally apparent should be the concept that since not all lesions progress during the natural history of carcinogenesis, there is an opportunity to influence the course of the disease. Fifteen years ago we first suggested that the domain of molecules composed of retinol (vitamin A) and its synthetic analogues, which we defined as retinoids, might be used as a pharmacological approach to the chemoprevention of cancer (12). The rationale for this approach was based on the ability of retinoids to exert a hormone-like control of normal cellular differentiation and proliferation in essentially all epithelia that are target sites for the development of invasive carcinoma (13). Furthermore, it had even been shown that retinoids could restore normal cellular differentiation to a dysplastic epithelium that had been initiated with a carcinogen (14). Since the process of carcinogenesis is fundamentally characterized by a loss or arrest of cellular differentiation (15, 16) and since retinoids intrinsically induce or enhance such differentiation (17, 18), we suggested that retinoids could be used as physiological, rather than cytotoxic, agents to arrest or reverse the process of carcinogenesis (12, 19, 20). This approach has been validated in many studies in experimental animals, and most importantly, by now there are significant clinical data to indicate that it is also applicable to humans.

Since retinol and its esters (the molecular forms of vitamin A that we ingest in our food) have undesirable pharmacokinetic and toxicological properties, it has been necessary to develop synthetic analogues for effective chemoprevention. More than 1000 retinoids have been synthesized by the organic chemists, and thus far the most useful ones for chemoprevention have been analogues of all-*trans*-retinoic acid. It is now known that all-*trans*-retinoic acid is the ligand for nuclear receptors that regulate gene function (21, 22), which adds further credibility to the hypothesis that chemoprevention by retinoids is mediated by physiological processes.

Studies in animals have shown that analogues of retinoic acid can block the development of invasive carcinoma at epithelial target sites including mammary gland, bladder, lung, pancreas, and skin (see Ref. 23 for a review); most recently, the prostate has been added to this list (24). Based on these findings in experimental animals, important clinical studies have subsequently demonstrated that 13-*cis*-retinoic acid can reverse premalignant lesions (leukoplakia) of the oral mucosa (25) as well as prevent the development of head and neck carcinoma (26) or skin carcinoma (27) in patients at high risk. The retinoic acid analogue 4-hydroxyphenylretinamide (fenretinide), an agent highly effective for prevention of mammary cancer in

experimental animals (28), is presently being evaluated in several thousand Italian women for prevention of breast carcinoma (29). Most importantly, it has been shown in this trial that a retinoid such as 4-hydroxyphyenylretinamide can be safely administered for as long as 5 years to a cohort of women, with essentially no serious toxic side effects.

In addition to the retinoids, there are many other steroids or steroid analogues now being evaluated as potential agents for chemoprevention. Most notably, the estrogen analogue, tamoxifen, widely used in patients as adjuvant therapy for advanced breast cancer, has also been shown to be an effective agent for chemoprevention of mammary cancer in the rat (30, 31). Furthermore, other data indicate that tamoxifen and 4-hydroxyphenylretinamide can act synergistically to block progression of carcinogenesis in the rat mammary gland (32). The above results provide a strong rationale for the clinical evaluation of tamoxifen, either alone or in combination with a retinoid, for chemoprevention of breast cancer (33–36).

Conclusions

Over the past 25 years, death rates have remained unacceptably high and 5-year survival rates unacceptably low for most common forms of metastatic carcinoma, in spite of a huge investment of effort in the development of cytotoxic drugs. There has been a faulty perspective of the nature of the disease that we are trying to eradicate, focusing effort on the fallacious notion, enunciated by the National Cancer Institute in 1966, that "there now exists a logical, unifying theme for *control* [*italics* mine] of cancer in animals and man, namely that cure can be realized *only* [*italics* again mine] when all tumor cells are killed (37)." Thus, for 25 years there has been an obsession with the development and use of agents that kill cells (manifested most recently with the concept of dose intensification) for treatment of end-stage carcinoma. Although this approach has been highly successful for a few types of malignancy, it has in general failed to provide widespread cure for the most common cancers. As we learn more about the heterogeneity of the tumor cells that comprise a primary epithelial neoplasm and its associated metastases (5–7), the conceptual inadequacies of the cytotoxic approach to cancer cure become increasingly apparent.

A new perspective is therefore necessary, emphasizing that carcinogenesis is fundamentally an evolutionary process of aberrant cell differentiation. As modern techniques of molecular biology progressively elucidate the molecular and cellular basis for the multiple stages of carcinogenesis that occur before the development of invasive and metastatic lesions (38), it should become possible to apply this new knowledge to arrest or reverse the further development of early lesions. Pragmatically, we can no longer afford to ignore the biological significance of these early lesions. We must consider the entire process of carcinogenesis from its very inception, rather than using the antiquated conceptual framework and nomenclature that originated more than a century ago and that still dominate current thought about cancer. Greater effort must be given to development of new methods for detecting individuals at increased risk and to development of more accurate diagnostic markers, both of which will provide a more meaningful definition of the various stages of carcinogenesis and their relationship to invasive carcinoma. Ultimately, this new perspective will lead to some form of control of carcinogenesis during its earliest, preinvasive stages. Chemoprevention is not merely an idea whose time has come, it is now a clinically validated approach to the control of invasive carcinoma. It is now our responsibility to use this new discipline in the most clinically effective manner.

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