Cancer Chemother Pharmacol (2001) 48 (Suppl 1): S4–S10
DOI 10.1007/s002800100298

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Can we conquer cancer in the twenty-first century?

Abstract The twentieth century recorded the greatest advance in the control of human disease. From the beginning of recorded time, the human life-span changed little until the twentieth century. In the USA, it increased from 47.3 years in 1900 to 76.4 years in 2000. The answer to the question of "Can we cure cancer in the twenty-first century?" requires an appreciation of the contemporary nature of our knowledge. At the beginning of the twentieth century, major problems were nutrition and infection. By 1950, the major causes of mortality and morbidity were still infectious diseases, such as syphilis, tuberculosis, poliomyelitis, and influenza. The 1950s and 1960s were the golden age of control of infectious diseases, while cancer, because of the aging of the population and the strong association between cancer and age, has become the major healthcare problem of the twenty-first century. Until 1960, no one had proposed or demonstrated that a systemic or metastatic form of cancer could be cured. In only 35–40 years not only have techniques for the early detection, prevention, and surgical and radiation therapy treatments improved, but at least 15–20% of patients with systemic/metastatic cancers can be cured with our current primitive systemic treatments. Prior to 1943, there was no chemotherapy. Prior to 1948, no one had described complete regression of a systemic cancer. There were no multi-institution, randomized clinical trials prior to 1949. Additionally, combination chemotherapy, new drugs, bone marrow transplantation, broad-spectrum antibiotics to control infections, and platelets to control hemorrhage have been added in the past 50 years. The pace of progress extrapolates to a prediction of cancer control in the twenty-first century. The human genome has been sequenced, and it will be possible to identify expression profiles not only for malignant cells but for their normal counterparts. It is certain that interventions specific for control of the malignant transformation will be identified. An example of gene-directed therapy is in acute promyelocytic leukemia where *trans*-retinoic acid is effective and contributes to cure. The signal transduction inhibitors, small molecules bioavailable orally and specific for interfering with signals resulting from ligand-receptor interactions, are a dramatic advance. Because cancer is a genetic disorder, the expanding field of genomics will certainly accelerate our progress toward the control of cancer. Finally, the twenty-first century will be an era of enhanced communication. The computer has given us the internet. Our communication in cyberspace is not only universal but instantaneous. Increases in the speed at which knowledge can be exchanged and the enormous capacity for storing new knowledge in cyberspace ensure that the pace of progress that we saw in the twentieth century will accelerate in the twenty-first. To address the question in the title of this paper, I believe that it is not a question of whether, but only of when.

Keywords Cancer · Aging · Treatment · Prevention · Prediction

This work was presented at the 16th Bristol-Myers Squibb Nagoya International Cancer Treatment Symposium, "Hematologic malignancies: pioneers in cancer therapy across the century from mustard to molecular targets and beyond," 27–28 October 2000, Nagoya, Japan.

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Introduction

At the beginning of the twentieth century our knowledge of biology and medicine was primitive by the standards of today [4]. The median expected life-span at birth was only 47 years and the major life-ending and morbidity-causing illnesses were the infectious diseases, i.e. tuberculosis, syphilis, poliomyelitis and rheumatic fever, and nutritional deficiencies. Thus it is only over the past

100 years that we have seen the introduction of aspirin, Dr Paul Ehrlich's conception of antigen-antibody reactions and his discovery of the concept of chemotherapy, and the idea that a synthetic or natural chemical could affect human disease, such as the first use of nicotinic acid to cure pellagra in 1916, and vitamin C for the treatment of scurvy in 1930.

The golden age of the discovery of therapy for human disease occurred during the Second World War with the discovery of sulfachrysoidine and the sulfonamides as chemotherapy for infection, penicillin with its dramatic effect on infections including syphilis, streptomycin, and its virtual elimination of tuberculosis, and the introduction of chlorpromazine, which emptied the psychiatric hospitals. During the author's internship in 1949, the major illnesses treated were rheumatic fever with valvular heart disease, influenza, meningitis and meningococcal meningitis, pulmonary tuberculosis (in 1949, 85% of the more than 3 million people living in the city of Chicago, Ill., were tuberculin-positive), venereal diseases (i.e. syphilis and gonorrhea), and senile dementia.

An occasional patient with cancer was seen, but at the halfway point of the twentieth century, cancer patients were treated exclusively with surgery. If and when surgery failed to control the disease, the patients were relegated to the same palliative-care group as the elderly. At this point in history, radiation became a significant therapeutic modality with the introduction of high-energy radiation, specifically cobalt radiation therapy. However, the idea that a cancer that had spread beyond the possibility of control by surgery or radiation could be treated with any form of systemic therapy was not imagined as late as 1940. The popular notion was that since cancerous tissue had the same genetic and cellular composition as other host cells, it would never be possible to find a systemic agent that could distinguish between a cancer cell and a normal cell.

The analogy repeated in the 1950s was that a systemic therapy that would dissolve the left ear and leave the right ear intact could not be invented. The first hint of systemic therapy for cancer was the Nobel Prize-winning observations made by Dr Charles Huggins at the University of Chicago in 1940. He discovered that oophorectomy could result in temporary regression of breast cancers. He reported 1 year later that castration of males could result in temporary regression of prostate cancers. This indicated for the first time that there might be treatments for systemic cancers and that metastatic cancers were dependent on host factors.

A major breakthrough in cancer treatment occurred in 1943. Drs Louis J. Goodman and Alfred Gillman, University of Utah School of Medicine, reported that the alkylating agent nitrogen mustard could induce temporary regression of lymph node enlargement in patients with malignant lymphoma. When their report was published, it did not receive a great deal of attention, but in retrospect this was a phenomenally important contribution [1]. First, the authors established that chemotherapy could provide palliation for a systematic malignancy and they came to this conclusion through a systematic series of studies. It began with the study of nitrogen mustard gas, which was designed as a vesiccant to create pulmonary edema as a biological weapon. In addition to the effect on the lung, it resulted in severe aplasia of the entire lymphoid organ.

These brilliant investigators pursued this observation in experimental animals by administering nitrogen mustard parenterally, confirmed that involution of lymphoid tissue occurred, and described the pharmacology of the drug and the dose response. They transferred this information from experimental animals to the clinic in a systematic way and reported not only temporary regressions, but also that recurrences could be treated again. However, they clearly documented that the tumors became progressively resistant to the agent that they were administering. The concept of drug resistance was thus described at the same time that effective therapy was introduced. This observation was followed by the development of several alkylating agents that had a limited spectrum of activity. One important alkylating agent was busulfan, which was active when given orally and became the standard treatment for chronic myelocytic leukemia (CML) in which it regularly induced clinical and hematologic remissions [2].

In 1949, Dr Sidney Farber at Harvard University described a new approach to the treatment of cancer. He used the drug aminopterin as a folic acid antagonist, which was the first antimetabolite to be developed in preclinical experimental models and transferred directly to the clinic. Dr Farber, in childhood acute lymphoblastic leukemia (ALL), described the induction of clinical and hematologic remissions, and he introduced the concept of complete remission. However, he observed that these improvements were transient and the disease recurred in all patients. He also noticed that the recurrences became progressively more resistant to chemotherapy.

In 1953 Nobel Prize winners Drs George Hitchings and Gertrude Elion, Burroughs Wellcome, New York, synthesized the purine antimetabolite 6-mercaptopurine. Clinical studies reported by Dr Joseph Burchenal at Memorial Sloan-Kettering Cancer Center, New York, added another antimetabolite that could induce complete remissions in childhood ALL to the therapeutic armamentarium. This was followed by the reports by Dr Olaf Pearson at Memorial Hospital, New York, and of Dr Sidney Farber at the Children's Cancer Center in Boston, Mass., of remissions induced by adrenal corticosteroids.

The availability of three active agents for the treatment of childhood ALL led the group at the US National Cancer Institute, Bethesda, Md., under the leadership of Dr C. Gordon Zubrod to apply the concepts of combination chemotherapy that had been developed for infectious diseases to the treatment of ALL. In 1962, Dr Irving Johnson and the group at the Children's Cancer Research Center, Boston, and the US National Cancer Institute demonstrated that the vinca

alkaloid vincristine could also induce complete hematologic remissions in childhood ALL, and importantly, that the dose-limiting toxicity was not myelosuppression but neurotoxicity. This important addition to the therapeutic armamentarium led the National Cancer Institute group to develop the multiple agent/combination chemotherapy regimen (VAMP) which combined the four active drugs. To prevent the recurrence of disease, they intensified these remissions and demonstrated that remissions could be prolonged by repeating this chemotherapy in remission.

Another important development, which was led by the group at the National Cancer Institute, was the concept of objective quantitative criteria for response, the development of flow sheets and meticulous record keeping, and the application of modern statistical concepts to the quantitative evaluation of clinical trials. This led to the need for increased sample sizes, and the first cooperative group (Leukemia Group B) was formed by a collaboration between the National Cancer Institute and Roswell Park Memorial Institute, Buffalo, N.Y., under the leadership of Dr James Holland. This group rapidly accumulated members from other institutions and became an effective clinical trial technology for advancing the knowledge of the treatment of cancer. In a major and important study, the Leukemia Group demonstrated that the use of an agent active for induction of remission was even more effective when administered to patients in remission. This was the first adjuvant chemotherapy study and it became an important principal for the eradication of residual disease.

Based on the results of subsequent studies using multiagent combination chemotherapy for induction, early intensification, and intensive reinduction as maintenance therapy, in 1962 the group at the National Cancer Institute made the claim for the first time that the systemic metastatic cancer of childhood, ALL, could be cured with chemotherapy. That claim has been well verified. Another important event that occurred in the early 1960s was the description by Drs Min Chiu Li and Roy Hertz of the US National Cancer Institute of the cure of choriocarcinoma in females. This cure was accomplished because of the recognition that the chorionic gonadotrophin served as a tumor marker for residual disease. This led not only to the cure of choriocarcinoma, which is an allograft, but also to the cure of testicular cancer in males, which is a syngeneic tumor.

Cytogenetics and molecular genetics

The first accurate description of the morphology of human chromosomes was reported by Drs J.H. Tjio and A. Levan, US National Cancer Institute, as recently as 1956. Prior to that, it was commonly taught that humans had 48 chromosomes, and the clear demonstration of the morphology and the characterization of the 46 human chromosomes was first made less than half a century ago. The impact of this observation on cancer was first reported in 1960 when Drs Peter Nowell and David Hungerford, University of Pennsylvania and Fox Chase Cancer Center, described the Philadelphia (Ph) chromosome, a tiny loss of genetic material from the long arm of the smallest chromosome, chromosome 22. These investigators were enthusiastic about this finding because they reported that ten consecutive patients with CML had the same chromosome abnormality, and they proposed that every human malignancy would have a specific chromosome abnormality that could be identified morphologically. They chose the name Philadelphia1 to allow for Ph2, -3,and -4, which have not been described.

The impact of this observation on the field of cancer therapeutics was profound. First, when a large number of patients with CML diagnosed clinically were examined, it was found that there were patients who lacked the Ph chromosome. Approximately 10–15% of patients had apparently normal cytogenetics. After the genetic components of the 9:22 translocation were identified, the application of the reverse transcriptase polymerase chain reaction (RT-PCR) detected the genetic abnormality in patients who lacked the morphological abnormality, indicating a masked translocation. These patients had the same natural history and response to therapy as patients who had the morphological translocation 9:22.

From a therapeutic viewpoint, the most important observation was that when busulfan therapy was administered to achieve a complete hematologic remission, examination of the bone marrow revealed that virtually all of the metaphases still had the Ph chromosome. This indicated that the leukemic stem cells could differentiate into platelets, red cells, and granulocytes, but the effect of this therapy was only palliative because the disease apparently persisted. This was associated with the clinical observation that 85% of patients who were treated with busulfan converted to an acute form of leukemia, so-called blastic transformation, and the median lifespan following diagnosis was only slightly prolonged by the use of the alkylating agents.

Thus the criteria for response had shifted from clinical and hematologic to cytogenetic criteria for response. Subsequently, the discovery that interferon could induce cytogenetic remissions and that patients who achieved cytogenetic complete remissions had a significant prolongation of life supported the concept that the therapeutic target for this disease was elimination of the Ph chromosome. Dr Brian Druker, University of Oregan, Portland, and his group found that a signal transduction inhibitor designed to inhibit the translation of the BCR/ABL neogene is highly effective in inducing clinical, hematologic, and cytogenetic remissions of CML. This provides one of the potentially most powerful tools for the control of systemic cancers in the next century.

The story of the development of effective therapy for CML, that is, the identification of the cytogenetic abnormality and the conversion of that knowledge to the genetic basis for translocation, and the development of therapy specifically directed at this genetic

translocation, creates a paradigm for the development of cancer treatment in the future.

Impact of cytogenetics and molecular genetics on other malignancies

Following the description of the Ph chromosome, many investigators reported what appeared to be random changes associated with malignancies of various types. In 1974, it was recognized that nonrandom chromosome abnormalities were associated with specific clinical syndromes, which identified a small subset of patients who had the morphological and clinical diagnosis of acute myeloblastic leukemia (AML). The first to be recognized was the reciprocal translocation between chromosomes 8 and 21 (t8:21). First described by Drs Jose Trujillo, M.D. Anderson Cancer Center, Houston, Tx., and Janet Rowley, University of Chicago, Ill., it was recognized that these patients compared with other patients with AML, had a better prognosis and a morphological association with Auer rods, an organelle in the cytoplasm of the leukemic cells. This aneuploidy was found in only 6–7% patients with AML.

This was followed by the description of a number of nonrandom chromosome abnormalities, which identified different clinical syndromes within the diagnosis of AML. An important one was the translocation between chromosomes 15 and 17 (t15:17) associated with the morphological characteristics of acute promyelocytic leukemia (APL). Approximately 6–7% of patients with AML have this subtype. This abnormality was important because the breakpoint on chromosome 17 occurred within the gene for the receptor for retinoic acid, and it was subsequently shown that the administration of all-*trans*-retinoic acid in pharmacologic doses to these patients could induce hematologic remissions. This was probably the first example of gene-directed therapy with a small molecule.

It was soon recognized that although retinoic acid therapy alone could induce remissions, the disease regularly recurred and therefore the treatment was not curative. However, it did initiate an era of gene-directed therapy that eventually led to the design of other small molecules. An example of gene-directed therapy in solid tumors is the demonstration that Her2Neu overexpression is associated with poor prognosis in breast cancer which led to the development of trastuzumab, a significant advance in the treatment of this malignancy. It operates by directing therapy to a specific genetic abnormality associated with malignancy and is another paradigm for the future development of gene-directed therapy.

The t15:17 abnormality in APL is also important because the transcription product could be detected by RT-PCR and it can be used as a reliable predictor of residual disease, i.e. no detectable levels of gene expression after treatment are associated with prolonged patient survival, whereas persistence of expression at a given concentration reliably predicts persistence of disease and recurrence. This is also an important paradigm for the future development of gene-directed therapy, since the genetic abnormalities associated with malignancy can serve as important markers of residual disease. The example of the t15:17 in APL, however, is not consistent since the t8:21 abnormality can be detected by RT-PCR in a significant proportion of patients with AML who are both free from treatment and free from disease for more than 5 years and are evidently cured. Thus it is possible for residual t8:21 transcripts to be present without recurrence of disease.

In 1987 it was proposed that cytogenetics could provide a new classification system for AML. It proved to be the most important of all the known prognostic factors [3]. Approximately 20% of patients with AML can be characterized as having a favorable prognosis (t8:21, t15:17, and inversion 16). They have a high probability of response, improved survival time, and a detectable cured fraction. Another 25–30% could be characterized as having an unfavorable prognosis, with a low response rate and an essentially zero cure fraction (–5, –7, trisomy 8, and other complex cytogenetic abnormalities). Approximately 40–50% of patients have diploid cytogenetics, and their prognosis is intermediate between the favorable and unfavorable groups, suggesting that with more sophisticated techniques, molecular genetic abnormalities will be described in these patients.

The implications of these findings in AML for other solid malignancies is that we will progressively recognize that morphological diagnoses, i.e. breast cancer, colon cancer, etc., represent groupings of diseases that have different biologies that account for the heterogeneity of prognosis and response to therapy. Increasing investigation of the molecular genetic abnormalities in malignancy will undoubtedly clarify this heterogeneity and lead to innovative paradigms for therapy. As discussed above, all-*trans*-retinoic acid induces remission in virtually all patients with APL, but has minimal effectiveness in other myeloblastic leukemias. Similarly, cytosine arabinoside is the major active chemotherapeutic agent for inducing complete remissions and results in potentially cured patients who survive for 3 years or longer without evidence of recurrence of disease. Yet a significant number of patients with AML are not cured after treatment with this drug. Therefore recognition of heterogeneity will lead to therapy not only directed at the molecular genetic abnormality, but also to the identification of unique chemotherapeutic agents for each subset within the various malignant diagnoses. Moreover, we will learn that complete remission of clinically detectable disease is necessary but not sufficient for long-term disease-free survival. As the cytogenetic and molecular genetic bases for heterogeneity are recognized, they will prove, as in acute leukemia, to be important tumor markers for detecting residual disease and providing the indication for adjuvant therapy for patients who are otherwise in complete remission.

Supportive therapy

In the early 1960s, pheresis to collect the formed elements of the blood was introduced. This technology resulted in the introduction of allogeneic platelet transfusion and allogeneic white cell transfusion. Both components were essential to prevent morbidity and mortality from intensive chemotherapy and were particularly important for the development of the Nobel Prize-winning research of Dr E.D. Thomas, University of Washington, Seattle, Wash., in developing successful allogeneic bone marrow transplantation as therapy for patients with leukemia. Not only did the transplant prove to be curative for patients with acute leukemia, but it has also been observed recently that the infusion of donor lymphocytes in patients whose allografts failed to eliminate their leukemia, particularly patients with CML, can result in sustained complete cytogenetic remissions. This observation has stimulated the field of cellular immunotherapy and extended the potential for the use of immunotherapy for the control of other malignancies.

With the discovery of the cytokines, which regulate the proliferation and release of hematopoietic cells, it has been possible to mobilize sufficient stem cells to the peripheral blood. This is a new form of allogeneic transplantation using peripheral blood stem cells from donors instead of bone marrow. Particularly attractive is the use of autologous peripheral blood stem cells collected while patients have normal hematopoietic organs. This allows the use of high-dose chemotherapy to intensify the therapeutic intervention and potentially improve the effectiveness of systemic therapy for common malignancies. Although this technology is not yet proven, it provides a much broader area of support for systemic therapy in malignancies.

Cancer prevention

The most dramatic change in the occurrence of cancer in the twentieth century was the emergence of lung cancer as the leading cause of morbidity and mortality. In the early l950s, Dr E. Wynder, New York University, N.Y., demonstrated that the products of tobacco were carcinogenic in experimental animals. Subsequent epidemiologic studies have established that the use of tobacco is responsible for the epidemic of lung cancer. Tragically, efforts to control tobacco abuse have been only marginally successful. In the USA, legislation that provides smoke-free environments for nonsmokers and which limits the areas where smoking can occur, and limits the advertising and promotion of tobacco consumption, have been only slightly effective. Adult male smoking rates have declined significantly, and over the past 4 years there has been a decrease in the lung cancer rate in men.

Unfortunately, the situation in US women is different. Smoking as a socially acceptable behavior in women began approximately 30 years after men acquired this habit, and the epidemiologic pattern of smoking increase in women mimics that in the male population. Unfortunately, there has been no decrease in smoking among females. In adolescent females, the rate of smoking is actually increasing. Internationally the consumption of tobacco continues to increase. There has been a dramatic increase in developing nations in the abuse of tobacco products with an accompanying increase in cancers of the aerodigestive and urinary systems, as well as in peripheral vascular and coronary artery disease. This is an area where social action could provide an effective preventive strategy despite the fact that it has not been effective in the past 50 years. However, in the author's opinion, a curative treatment for lung cancer could be developed in the twenty-first century.

Association of cancer with host age

There is a small peak in the incidence of cancer in children at approximately 4 years of age, which includes embryonal tumors, ALL, and other malignancies associated with developmental abnormalities. However, the incidence of cancer becomes low during the teenage years and then rises exponentially to the age of approximately 70 years. By that point, the incidence of cancer per number at risk is several hundredfold that at the ages of 10 to 15 years. This strong association of cancer incidence with host age once relegated cancer to the category of a "disease of aging." However, Dr Al Knudson, at Fox Chase Cancer Center, Philadelphia, Pa., was the first to propose the "two-hit hypothesis," i.e. that more than one event is responsible for the occurrence of malignancy. The original observations were made in pediatric retinoblastoma when it was recognized that tumors occurring early in life were associated with a homozygous abnormality, whereas those occurring later were heterozygous and required a second environmental event. Thus at least two genetic events or one genetic and one environmental event are required to induce cancer.

The hypothesis explains the strong association between cancer incidence and age, since the likelihood of two events occurring concurrently increases the longer the host is at risk. What is not yet explained is the fact that the exponential increase in cancer incidence reaches a plateau after the age of 70 years, and appears to decrease slightly in the very elderly. One possible explanation is that some people are genetically resistant to carcinogens in the environment. The dramatic decrease in mortality from both coronary artery and cerebrovascular disease in the past 25 years has resulted in more than a 30% decrease in overall mortality. This resulted from an understanding of the etiology of atherosclerosis and the development of dietary, lifestyle, and pharmacologic approaches to correcting the causes of atherogenesis, coupled with major advances in the treatment of coronary artery disease and stroke. During

the same 25-year period, mortality from cancer continued to rise, mainly, although not entirely, attributable to the continuing increase in lung cancer mortality associated with tobacco abuse. However, the advances in therapy that began in the early 1950s have finally resulted in a decrease in the overall mortality (age-corrected) of cancer in the US population. The decrease in mortality, however, is largely confined to young adults and children.

The cancer mortality rates for patients less than 65 years of age now exceed the mortality rates from cardiovascular disease in the past 20 years. However, for patients over 65 years of age, although the mortality rate from cardiovascular disease has decreased by about 30%, mortality rates from malignancies have continued to show a slight but definite increase. This reflects the fact that cancers in later life are more malignant and more resistant to current therapies. This is particularly striking in the hematologic malignancies, in which response and cure rates are relatively high. It has been observed in almost all solid tumors that age has a negative prognostic effect on response to therapy and survival. This also suggests that there is a fundamental association between cancer and aging that remains to be defined.

The populations in the Western world are demographically shifting to higher ages, both in terms of the median age and the number surviving for long periods. Based on US Census Bureau estimates, the most rapidly growing segment of the population is centenarians. It is estimated that the number of people aged 100 years or older will triple within the next 20 years. The progressive shift of the population toward advanced age, associated with the strong association of cancer incidence and mortality with age, suggests that cancer will have a major impact on life shortening.

Since based on the results from the previous century the author is prepared to predict that cancer will be controlled in the next century, it is reasonable to ask what the effect of cancer control will be on the overall life-span. There are two prevailing hypotheses about human life-span. The first is that the human life-span, as in many other species, is finite and at some predetermined genetic time interval, life will cease [4]. Perhaps an essential component of the genome is depleted, e.g. telomere shortening. If cancer, like cardiovascular disease, is conquered, the shift in the median age will continue. Therefore, as we conquer the diseases that occur at each phase of the human life-span, the proportion of people who reach the maximum life-span will increase, but the maximum life-span will not change.

The alternative hypothesis is that all human life shortening is a result of disease, and if diseases that occur during each segment of the human life-span are conquered, the life-span will increase. It might be possible that immortality will be a consequence of disease control. There has recently been an important publication from Sweden that the maximum age at death in the Swedish population rose from a rate of 0.44 years per decade in 1860, but accelerated in 1969 to 1.1 years per decade thereafter [5]. This suggests that humans do not have an immutable life-span and that the control of common diseases that terminate life will increase not only the number of people, but the total life-span of humans. We have yet to learn whether the apparent decrease in cancer incidence after the age of 70 years will continue into the 11th and 12th decades of human life, but the author believes that these data predict that the control of cancer in the twenty-first century will lead to a significant increase in the maximum attainable age.

Who predicts the future?

When polling individuals who are not scientists about the potential improvements in the human condition in future years, the usual prediction is that there will be slight but not dramatic change in our knowledge and lifestyle. It has been repeatedly demonstrated that the general public has limited ability to imagine the type of innovation seen in the twentieth century (Fig. 1). In contrast, scientists who have learned that the best predictor of the future is extrapolating from the past predict that the pace of change observed in the past will almost certainly continue in the future. However, the majority of scientists have limited ability to evaluate the rate of change that has occurred in the immediate past. They view such changes as linear, and therefore their projections are usually linear. That is, they predict that the rate of progression in knowledge and lifestyle in the future will proceed at the pace that it has in the recent past. Science fiction writers have consistently anticipated the dramatic changes that have occurred in civilization. They have imagined space travel and humans on the moon, jet engines and rapid speed, and the internet and the ability to communicate in cyberspace.

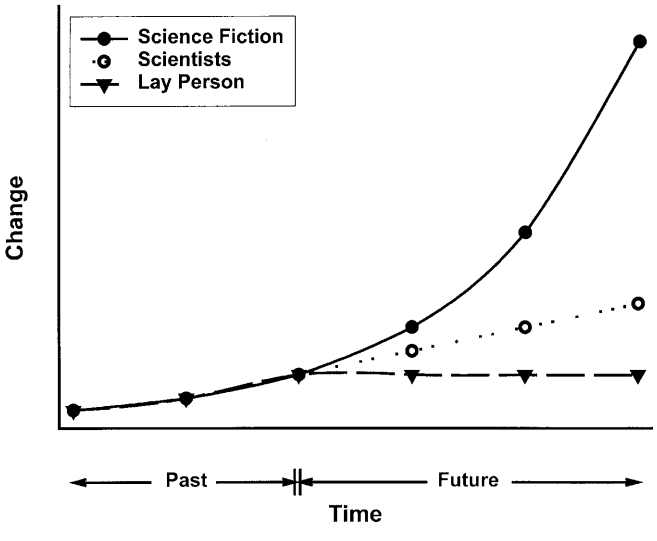

Fig. 1 Predictions of future life expectancy among lay people (▼), scientists (○), and science fiction writers (●)

The expansion of our knowledge base and progress in the human condition have occurred at an exponential rate because as fundamental knowledge accumulates, the opportunities for new scientific discoveries are enhanced in proportion to the amount of knowledge. Therefore, an exponential increase in knowledge is the prediction most consistent with the past. If an extrapolation to the twenty-first century is made on the basis of the rate of change in the twentieth century, the author is confident that cancer will be controlled in the same sense that infectious diseases have been controlled. It is likely that physicians will have at their disposal the protein products of all 100,000 genes, with the ability to regulate cell proliferation and differentiation. We will see the development of small molecules that can interact with each of these proteins in a specific way, regulating both the expression and effect of each protein in the human organism. If the current knowledge base on human genetics is coupled with the enormous pace of development of computer science, the internet, and sophisticated communication methods among individuals, it is reasonable to predict that cancer will be controlled in the immediate future. The essential ingredients of such an intellectual achievement will be maintaining world peace, progressively elevating the standard of living of the entire human population, and devoting our energies to the control of human disease and suffering. At that point, we should be able to test the hypothesis that the human life-span is finite, or discover whether it is infinite.

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