The Future of Clinical Cancer Research in the Next Millennium

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Introduction
I was profoundly honored and grateful to Dr. Evan Hersh and the organizing committee of this symposium, both for their efforts in organizing this excellent program and for their invitation to discuss the future. Because none of us is clairvoyant, I believe the best prediction for the future is based on an extrapolation from the pace at which clinical research has proceeded in the past. My own clinical research career has spanned 44 years. I can appreciate the enormous pace at which clinical cancer research has advanced in that one professional lifetime. Two such professional lifetimes, that is, 88 years, would take us back to 1909, approximately the turn of the century. It was then that two major individuals made an impact on the next 88 years of clinical research. The first was Paul Ehrlich, the first scientist to conceive of chemotherapy. The notion that chemicals, either natural or synthetic, could be used to treat human disease was followed by a series of brilliant empirical experiments, both in vitro and in laboratory animals, which led to the discovery of salvarsan. This was the first effective therapy for disseminated syphilis, which plagued our species at the turn of the century. Dr. Ehrlich also discovered the acid-fast stain for tuberculosis and made important observations that led to the formulation of the lock-and-key hypothesis of immunology, which began another whole branch of clinical science.

The other important event at the turn of the century was the Flexner Report, written by a Ph.D. scientist, Dr. Abraham Flexner, who did a systematic study of medical education in the United States under the auspices of the National Academy of Sciences and issued a report that led to the medical curriculum we all have experienced in our training. He showed the necessity to have basic science in addition to the apprentice-type clinical training that was customarily the backbone of physician education at the turn of the century.

During the second World War, a major threat to the health of the American soldiers who fought in the Pacific was malaria. The military undertook a crash program that was based on the development of an effective animal model, synthesis and screening of natural and synthetic chemicals against the malaria parasite in animals, and rapid transfer to clinical trials. This was a successful program and was reputed to have made a major contribution to our ability to emerge successfully from the war. Immediately after the war, there was a renaissance in clinical research that was sparked by not only the malaria discovery but the discovery of chemotherapy for microbial diseases and the antibiotics, particularly penicillin, for the control of infectious diseases. In 1948, the first publication of a prospective randomized clinical trial appeared, the study of streptomycin for the control of tuberculosis. Prior to the war, some forward-looking individuals had decided that the NIH, which was located on a lovely campus in Bethesda, MD, might have added to its many well-developed laboratories a hospital, “a clinical center.” The concept was to have patients and laboratories in intimate contact and to staff this hospital with physicians who conducted clinical research as their major activity. Dr. James Shannon, who had worked on the malaria product during the war, was appointed the Director of the NIH, and he attracted many outstanding clinical investigators, including Dr. Gordon Zubrod, who was recruited to the NCI.

After I completed my internal medicine training in 1953, I moved to the Boston University School of Medicine (Boston, MA) to work in a laboratory under Drs. Joseph F. Ross and Stewart C. Finch to discover the kinetics of hematopoietic cell turnover with the use of the newly available radioactive isotopes that came from the atomic war effort. The president of the Boston University School of Medicine, Dr. Chester Scott Keefer, had created a research-oriented hospital, the Massachusetts Memorial Hospital, where young academic and scientific clinical scientists were able to do clinical research in close proximity to their laboratories. This was the environment where I received my hematology training. Dr. Keefer was chosen to be the first Undersecretary for Health by the first Secretary of Health, Education and Welfare, Ovita Culp Hobby, from Houston, Texas. Dr. Keefer was responsible for helping to staff the newly opened clinical center of the NIH. He suggested that I fulfill my military obligation by moving to the NIH. Dr. Zubrod had already recruited Dr. Emil Frei III from St. Louis University (St. Louis, MO). Dr. Zubrod offered me a position in the NCI in 1955. The next 10 years was a period of enormous innovation and productivity. As a result, in 1965, Dr. R. Lee Clark, the founder of The University of Texas M. D. Anderson Cancer Center, attracted first Dr. Frei and subsequently me to come to this institution, where we worked together until 1972, when he was recruited to the Harvard Medical School to head the Dana-Farber Cancer Institute (Boston, MA). The decade from 1965 to 1975 was also highly productive. Many of the best and brightest young physicians were attracted to clinical cancer research, not only in Bethesda and Houston but in the academic medical...
centers throughout the land. Medical oncology became an approved subspecialty of internal medicine, and the number of young physicians moving toward clinical cancer research corresponded to the enormous opportunities for making rapid progress in this field.

In 1976, I was honored to be selected as the seventh individual to receive the David Karnofsky prize from the American Society for Clinical Oncology. By that time, now more than 20 years ago, I was becoming progressively concerned about forces that were impeding clinical research and detracting from the attractiveness of such academic careers for young physicians (1). I devoted my lecture to an analysis of these problems and suggested solutions. One year later, in 1977, at the meetings of the clinical societies, Dr. Samuel Thier, the president, also called attention to this emerging problem. “The endangered species today is not the primary care physician but the M.D. investigator” (2).

By 1980, Dr. Thier had chaired a prestigious committee of the Association of American Medical Colleges, which published a report that included: “the physician investigator possesses unique capabilities and perspectives that form the ‘bridge’ between the research laboratory and the bedside” (3). Also in 1979, Dr. Wyngaardan, who became Director of the NIH, published an often quoted paper in the New England Journal of Medicine reiterating the phrase “the clinical investigator as an endangered species” (4).

My good friend and professional colleague, Dr. Emil Frei, was chosen to give the Karnofsky Lecture in 1981, and he chose to devote his lecture to the topic “Clinical Cancer Research: an embattled species” (5). These early warnings from prestigious clinical scientists had no impact, and the problem continued to escalate.

In January 1990, I had the opportunity to serve as a special assistant to the then Director of the NCI, Dr. Samuel Broder. Dr. Broder was particularly concerned about the problems in clinical research as it related directly to the cancer problem. Therefore, he suggested I devote the year to a study of the status of clinical cancer research in the United States (6). The strategy we chose was to emulate the classic study of Dr. Flexner in 1910. I visited 20 of the leading comprehensive cancer centers in the United States. The visitation part of the project covered approximately 4 months. The usual visit, consisting of 2.5 days, included meetings with the center director, the training program director, senior faculty, junior faculty, and the fellows as a group and several interviews with fellows who were chosen from the training class in the group. These 20 centers made up approximately half of the designated comprehensive cancer centers in 1990, and these institutions were responsible for training 29% of the physicians in approved programs of the Accreditation Council for Graduate Medical Education. This study confirmed that there was in fact a continuing decrease in the quality and quantity of young physicians entering the academic careers in clinical oncology research. We defined this discipline as cancer research requiring an interaction between a clinician and a patient. We identified two major contributing factors to this decrease: the poor academic status of their role models in the academic institutions and the strong and widespread perception that funding for clinical oncology research was at a competitive disadvantage with laboratory-based research. We therefore made two major recommendations. The first related to an improvement in opportunities for training in clinical cancer research, and the second, and perhaps more important, to “develop peer review mechanisms that allow clinical cancer research proposals to compete within a pool restricted to proposals in this category.” Implementation of such a recommendation would require development of a clinical oncology research study section.

The balance of my year was spent in an effort to implement these recommendations. The NCI held a workshop of over 30 prominent investigators that was organized and conducted by Dr. Brian Kimes, who was administratively responsible for the training programs. The results of this workshop were published in 1991 (7) and led to a round of training program grant awards specifically designed for clinical investigators. In addition, a Request for Proposals was issued to determine whether there was a need for additional funding in clinical research. The response to the Request for Proposals was overwhelming, such that only a small fraction of the approved applications could be funded. Also during that year, the data were presented to the National Cancer Advisory Board, and the NCI workshop committee also recommended to the Director of the DRG and to the Director of the NIH that a study section be established for this purpose. In 1992, Dr. Edward H. Ahrens, Jr., published a brilliant and scholarly book which called attention to the “crisis in clinical research” (8). Dr. Ahrens studied the problem deeply and objectively for several years. He followed up the book with the publication of a patient-oriented research newsletter. He collected and submitted to the DRG at NIH the names of over 100 clinical research scientists who would be willing to serve on a study section and who had never served on such study sections. Speaking for myself, I have never been invited to serve on a study section of the DRG in my 44 years of full-time clinical cancer research.

In 1993, the DRG itself commissioned yet another study. This was a clinical research study group chaired by Dr. Gordon H. Williams that included 11 prestigious members. I was given the opportunity to testify before this study group, along with many other clinical researchers who had either published or expressed concern about this problem. The final report was issued in November 1994, and it was published in summary form (9). The entire report, which covered two grant cycles, is available from the DRG. This study demonstrated yet again, clearly and objectively, that proposals that had a clinical component requiring an interaction between a patient and a physician had a significantly lower success rate than laboratory-based proposals or proposals that dealt with human tissues or cells in the laboratory.

Six months later I made a great discovery. I was invited to a meeting of the NCI Board of Scientific Advisors, Clinical Trials Review Group created by the new NCI Director, Richard Klausner, held on October 9, 1996. At this meeting, the reports of the Institute of Medicine and the Nathan Committee were presented, as well as the results of the Gordon Williams Committee, and I had an opportunity to summarize the results of the study I conducted in 1990. However, the most lucid commentary was made by Dr. Arthur H. Rubenstein, who has served as Chairman of the Department of Medicine at the University of Chicago College since 1981. He suggested that continuing to
study the problem of "the endangered species" and issuing reports, calling for solutions by the NIH or other major funding organizations, specifically, creating appropriate peer review groups for clinical research and setting aside appropriate funding for training, retention, and subsequent funding of clinical research. Such recommendations have now been made continuously by scholarly groups of clinical investigators beginning in the late 1970s. Despite repeated recommendations from these prestigious groups the situation is, if anything, worse than it was twenty years ago. Dr. Rubenstein indicated that the people who charged these committees and sought these recommendations did not seem to have the will or desire to implement them. It seems evident that if they did, there are sufficient data and recommendations to have acted on this long ago. Therefore, we should stop taking such endeavors too seriously and instead focus on innovative ways to approach this problem.

What should that strategy be? In this paper, I propose that the enormous expansion of basic science knowledge on the one side and the enormous social burden of cancer on the other will provide the stimulus necessary to salvage and strengthen the "bridge," i.e., clinical research, caring for cancer patients.

**Advances in Basic Science**

The basic science side of the chasm is characterized by an explosive increase in our knowledge of the molecular mechanisms of disease. Because my career-long scientific interest has been in the disease human leukemia and because these diseases have played a leading role in elucidating the molecular basis of malignant disease, I will focus on leukemia (10). The new generation of molecular medicine began in 1960 with the discovery by Drs. Peter Nowell and David E. Hungerford that the shortening of what was then the long arm of one of the smallest human chromosomes (i.e., either chromosome 21 or 22) was associated with a specific hematological malignancy, CML (11). We currently know this abnormality is not a loss of genetic material but a reciprocal translocation of chromosome material between chromosomes 9 and 22. The piece from the long arm of chromosome 9 contains a major portion of the oncogene ABL juxtaposed to a major portion of another gene on chromosome 22, which has been called the BCR because the breakpoints are not in a consistent location. The result of this reciprocal translocation is a "neogene" known as the BCR/ABL gene. This neogene is unique to the tumor and does not exist in the other somatic cells in the affected host. Thus, we had finally found a tumor-specific abnormality. Furthermore, we now know that this neogene is important to the entire natural history and biology of CML (12). The first important observation was that it is fundamental to the diagnosis of CML because patients who have a similar spectrum of clinical and hematological changes but do not have the Ph chromosome are now recognized to have a different biology and different natural history of their disease.

In patients with acute leukemia, particularly acute lymphoblastic leukemia, the presence of the Ph chromosome is usually in a different location on the BCR gene resulting in a slightly altered neogene, and again is fundamental to the basic biology of this disease because it is uniquely resistant to otherwise effective chemotherapy. But perhaps the most important observation about the Ph chromosome is that it now forms the surrogate end point for therapeutic intervention. Treatment with alkylating agents may produce complete clinical and hematological remissions, yet they do not significantly prolong survival. However, treatments that suppress or eradicate the neogene BCR/ABL are regularly associated with both significant prolongation of survival and in many instances fulfill the criteria for a cure. The first application of the reverse transcription PCR test to expand the sensitivity of molecular methods for detecting small amounts of residual genetic material was published for this disease (13). This test has proven to be extremely important in detecting residual disease and predicting for recurrence versus cure.

The discovery of this unique neogene specific to the tumor cells of CML suggested that each of the many hundreds of different cancer diagnoses might well have specific genetic changes associated with and identified in those tumors. The obvious first candidate for such a neogene was AML. However, early studies revealed changes that appeared to be random and therefore could conceivably have been secondary to the malignant transformation process. We now recognize that the specific genetic changes, although varied in AML, have in common with the Ph chromosome the fact that the nonrandom chromosome abnormalities that have been identified have specific clinical syndromes associated with them and specific prognosis and response to therapy. The most striking example is APL, in which there is an associated reciprocal translocation between chromosomes 15 and 17, resulting in two neogenes, both of which are transcribed. The discovery that all-trans-retinoic acid could induce remissions of this disease, a clinical observation, led to the laboratory identification of the breakpoint in the retinoic acid receptor α gene. As with CML, we now recognize that the PML/RARA neogene is specific to the APL tumor cells, is useful for the diagnosis, and serves as a surrogate marker for treatment that significantly affects the natural history of the disease. As with CML, molecular methods, such as reverse transcription PCR, have proven useful for detecting residual disease and influencing the strategy for treatment. APL makes up approximately 5% of the patients with acute myeloblastic leukemia. The other clinical syndromes, including the inversion 16 abnormality, the reciprocal translocation between chromosomes 8 and 21, join the t(15;17) disease as making up the 15% of AML patients who have a favorable response to treatment and have a substantial cure rate as measured by 3-year disease and treatment-free survival. At the other extreme, patients with deletions or loss of the long arm of chromosomes 5 and 7 or a trisomy of chromosome 8 have a uniquely poor prognosis and respond badly to currently known treatments. The consequence is that cytogenetics and molecular genetics has become the single most important factor in diagnosis, prognosis, and the choice of treatment for acute leukemia.

Although the molecular biology of cancer has had a robust beginning (14), it is clear that we have in hand the tools to embark on a project to clone the entire human genome and, as a parallel activity, to identify the crucial molecular events unique to each of the cancers in humans. The language of medicine for the next millennium is clearly molecular. The new era in medicine is the identification of the molecular basis for the genetic and acquired diseases of humans, and of course, cancer is fundamentally a genetic disease in which an alteration...
in a somatic cell is faithfully reproduced to create a clone of malignant cells able to destroy the host.

It is not necessary to expand here on the rapid progress in our understanding of the basic biology of cancer, which is certain to continue at an ever-accelerating rate, as it has over the last 37 years. But it is necessary to realize that what we have seen in the past will be modest and slow compared to the development of knowledge in the immediate future because we are also living in an era of "cyberspace." Where in the past we had to move paper, where new research findings appeared for general distribution months to years after their discovery, where knowledge dissemination depended upon mail (the physical movement of paper) or upon meetings and symposia (the physical movement of human beings), in the future, knowledge will move in cyberspace. Communication can be instantaneous. New knowledge can enter the scientific communication stream without delay. The rapid progress in computer science, which has put the power of the workstation at the control of individuals in their offices, allows enormously rapid, efficient, and effective access to the pool of knowledge that now exists and that will be created in the future. So as I peer from the background of the scientific accomplishments of the past generation toward the expected productivity of the next generation of scientists, my prediction is, as it should be, for an exponential rate of the accumulation of knowledge about the biology and physiology of the human species and of its diseases, and cancer in particular. Thus, I am confident the scientific side of the chasm will continue to grow at an exponential pace over the next 44 years.

Cancer as the Most Important Health Care Problem in the Next Millennium

Cancer is strongly associated with age. There is a small peak in cancer incidence at the age of 4–5, which still makes cancer the leading cause of both major illness and death in the pediatric age group. This peak disappears by age 15. But between the ages of 15 and 65, the increase in the incidence of cancer is exponential. The incidence by age 50 is 100 times the incidence at age 15. As far as can be seen, the frequency continues to increase for as long as there is estimated lifetime (Fig. 1; Ref. 15). Mortality rates for cancer also show a similar strong relationship to age, but the effectiveness of treatment has clearly been evidenced by a detectable decrease in mortality between 1973 and 1991. However, the major decreases in mortality have occurred in neoplasms that occur in young adults, such as testicular cancer, lymphoma, and leukemia. In contrast, the patient group over the age of 65, which has the highest incidence, has had a slight increase in the overall mortality per 100,000 patients at risk. At least in part, this results from a shift in mortality because of the effectiveness of palliative treatment for cancer, which prolongs survival and moves the interval between diagnosis and survival in a favorable direction. However, the curative treatments are largely for cancers that occur in the young.

The public health impact of cancer can be even more dramatically demonstrated by its effect on overall mortality when contrasted with the changes in mortality from heart disease (Fig. 2; Ref. 15). Over that 18-year period between 1973 and 1991, the mortality from neoplasms declined slightly for individuals under 65. In contrast, mortality from heart disease has declined dramatically in the same period of time. As a result, the rate of death from cancer has exceeded the rate of death from heart disease since 1982 for patients under the age of 65. In contrast, for patients over the age of 65, although deaths from heart disease have declined, deaths from neoplasms have increased slightly. Viewed another way, when all deaths from disease are considered for patients under age 65 in 1973, heart disease accounted for 27% of deaths and neoplasms for 21%. By 1991, these had essentially reversed, with heart disease accounting for 20% of deaths and cancer 26%. In contrast, for patients ages 65 and over, heart disease accounted for 45% of the deaths in 1973 but fell to 38% of the deaths in 1991, whereas neoplasms accounted for 16% of the deaths in 1973 and rose to 23% of the deaths in 1991.

This strong age association of both incidence and mortality from cancer is not a manifestation of the "aging process"; rather, this is consistent with the multiple-hit hypothesis of cancer pathogenesis. It is clear that the occurrence of a malignancy requires multiple events, some genetic, many environmental, and many unknown. Multiple events are involved in the initiation, promotion, and expression of a malignancy that threatens...
Ages Less Than 65

Heart Disease

Neoplasms

Ages 65 and Over

Heart Disease

Neoplasms

Fig. 2 United States mortality rates for heart disease versus cancer from 1973 to 1991.

the life of a patient. For events requiring multiple contributing events, the time at risk becomes a significant factor for the incidence of that event. The example I frequently use is automobile accidents: the likelihood that one will have an accident, which involves multiple causes, increases with the amount of miles one travels in an automobile.

The importance of the age association is that in the Western world, and particularly in the United States, the age of the population has been shifting dramatically (16). In 1820, the median United States population age was 16.7 years; by 1996, it was 34.5 years, more than doubling in a period of 176 years. The consequence is we now have 50% of the population over the age of 35, which is the age at which the dramatic increase in cancer mortality occurs. Moreover, the most rapidly growing segment of our population is the group of patients over the age of 85. In 1995, according to census figures, 12.8% of the American population was over 65, 1.4% over 85, and only 54,000 were over the age of 100. The census bureau projection for the year 2050, which is 50 years into the next millennium, is that the population over 65 will increase to 20% of the population; the population over 85 will increase to 4.6%, an increase of more than 3-fold; and the population over 100 will be 834,000, which represents a more than 15-fold increase.

If you compute the average number of years of life lost per person due to the major causes of death in the United States, cancer represents the leading cause of years of life lost due to illness; it is exceeded only by accidents as a cause of loss of years of life (Fig. 3). Thus, if we combine the increasing incidence in mortality of cancer associated with increasing age with the demographic figures on the age of the United States population, it is clear that for the next millennium, cancer will be the major public health problem facing the health care community.

Solutions

We have on the one hand an enormously successful campaign to enhance our knowledge about the basic biology of cancer, and this program has been and will hopefully continue to be a major scientific triumph. This is coupled with the growing importance of cancer as a problem for the health care industry and for the public health of our community. It is clear that what is needed is the bridge between these two important components of the cancer problem. The cancer clinical investigator provides the bridge between the laboratory-based basic research and the clinical trials and clinical practice of oncology in the community (17). Translation is not sufficient for effective development. The "bench to bedside" translation needs to be augmented by the "bedside to bench" flow of knowledge. This case has been made much more fluently by Dr. Samuel Thier, currently the President of Massachusetts General Hospital (Boston, MA), who, in a lecture delivered in 1994, pointed out, "a truly linear system of research (translation) does not describe biomedical research. There is an oscillation or a loop and if one tries to force the process to be linear or interrupts it at any point the system will run down" (18). Recently, Drs. Christopher R. Flower and
Kenneth L. Melmon have conducted an important study of the track record in developing effective new therapies for disease and they have emphasized the fact that the "focus on clinical management is the key factor that distinguishes a 'clinical champion.' They accelerate pharmaceutical innovation by defining and vigorously exploring novel targets for compounds for known apparent mechanisms of action" (19). Flowers and Melmon (19) have pointed out that a clinical investigator can serve as a clinical champion in moving important developments in the pharmaceutical industry to effective therapies, a role that the clinical investigator uniquely plays in contrast to clinical-trial type physicians and physician-scientists who are employed in the pharmaceutical industry or work in planning away from the bedside (19). As recently as January 13, 1997, Dr. Joseph L. Goldstein, a Nobel laureate in medicine, devoted the first James A. Shannon Lecture at the NIH to the subject "The clinical investigator uniquely plays in contrast to clinical management is the key factor that distinguishes a 'clinical champion.' They accelerate pharmaceutical innovation by defining and vigorously exploring novel targets for compounds for known apparent mechanisms of action" (19). He summarized the biotechnology industry in 1977: "On average one new gene is cloned and characterized each day, one new recombinant drug is approved by the FDA each year. To take full advantage of the opportunities created by basic research, disease-oriented research, and the biotechnology industry, we need a larger number of thoughtful, dedicated clinical scholars who care for individual patients and who have the time and resources to achieve a deeper understanding of normal and deranged function at the level of whole human beings." (20).

Having made a strong case for the important role of the clinical investigator in the development of effective control of cancer, coupled with having made the case for the cancer clinical investigator being a continuously embattled species with a progressively diminishing number both in quality and quantity, what are the solutions to this important dilemma? As already indicated in the "Introduction," to continue to call for more federal dollars for training and RO1-type grant support for clinical research is both impractical and unrealistic; it has not been effective after 20 years of effort by the most qualified experts in the field. Restoring the clinical investigator's academic status is an important component of attracting the best and the brightest young physician-scientists to a career in patient-oriented research. A key element in the success of this activity is the availability of adequate funds for cancer clinical research. I am personally politically conservative, and I therefore have great confidence in free-enterprise solutions to extremely complex problems and the enormous power of the democratic process. In this paper, I have tried to make a case for the great demand for clinical investigators, which is the first essential component of solving the supply and demand problem; i.e., the increased demand should result in an increased supply of cancer clinical investigators. I think that to a large degree that process is already under way. The "managed care crisis" has focused attention on the important role of the academic medical centers in the health care community. It is clear that patient care in a clinical research setting cannot compete at a price level with conventional care. Thus, the first phase of the managed care revolution has diverted health care dollars from the academic centers to the private practice setting. But it is clear that even the managed care industries themselves, which are currently extremely profitable, are becoming increasingly aware of the importance of clinical research to the maintenance of high-quality care. One can reason by analogy with other major industries: the automobile industry and the computer industry were both industries in which competition at the purely price level threatened the research establishment, but those companies that maintained an innovative thrust in their products quickly recovered their share of the marketplace. I believe that managed care is going to be the great friend of clinical research. I predict that managed care companies will quickly recognize that innovation is an important component of the quality of their product, and they will recognize that access to the clinical research community will be an important component of the product they sell to their consumers. As we all know, health care in this country is not a totally free-enterprise activity. The federal government, through Medicare and Medicaid, is now a major player in the health care industry. Thus the free-enterprise component of the industry is going to need assistance from the federal government, not in the form of diverting taxpayer dollars into the health care industry but in the form of ensuring a level playing field for the third-party supporters of health care. An analogy may be drawn with the automobile insurance industry, the utilities industry, or the radio and television industry—all, to efficiently provide service for the community, have required regulation by governmental organizations. This regulation is frequently in the form of mandates or licenses for approval.

In the United States, the health care industry now accounts for almost 13% of the GDP (Fig. 4). This has more than doubled since 1960. In contrast, the total health research dollars have actually diminished as a percent of the GDP from over 2% to
under 2% in the same period of time. Many health organizations, such as the American Cancer Society, the American Society for Clinical Oncology, and others, and legislators have publicly expressed the need for a mandated set-aside of a proportion of the health care dollars for research. I believe a strong case can be made to use these mandated set-asides to support clinical research. Mandates are important to eliminate any competitive disadvantage that might accrue to third-party organizations that are forward-looking enough to allocate a sufficient amount of money to clinical research to maintain the advancing effectiveness of treatment and prevention of cancer. Should these funds then be turned over to the NIH to be distributed by the usual study section method? I do not believe that would be an effective mechanism because the NIH has already developed a system that ensures that the great bulk of funds will flow to laboratory-based research, and any additional funding, I believe, will end up moving in the same direction. Rather, we need to create as a country a new administrative structure, something analogous to the National Academy of Sciences or the Federal Reserve Board, that is, a free-standing agency that is able to develop a granting mechanism that is parallel to the NIH mechanism but has the totally different requirements characteristic of clinical research. This organization could be established by law or by some interinstitutional agreement, as the pharmaceutical companies have done with the Pharmaceutical Manufacturers Association, or it could be operated as a contracted activity of the federal government. It is not the place of this paper to outline the specifics of such a funding proposal, but I think it is clear that the demand exists and that the solution can be generated from the enormous investment we make in health care in this country. Many academic clinical investigators have made the important point that it is certainly less expensive to receive conventional treatment in a private institution, but in the long run, it is more expensive to prescribe ineffective treatment than it is to increase our investment in clinical research and to develop and discover treatments that will substantially reduce the human cost of cancer and the dollar cost of health care delivery.

The job of the academic medical centers and the embattled clinical investigators is to differentiate our product. Our product is clinical research and innovation, and we have to convince both the public and our elected representatives that this problem requires immediate solution.

In addition, as a community, we must make a strong commitment to reducing the obstacles to effective clinical research. One major obstacle is clearly an excess of regulation. On July 28–29, 1995, I attended another of a long series of meetings designed to address the problem of the long delays in drug approval times (21). As recently as 1995, the time to develop a new chemical entity for approval for the marketplace was in excess of 9 years (22). What is important is that the clinical phase makes up 7 of those 9 years, and the situation has been escalating. Moreover, the enormous financial investment in maintaining a drug development program is discouraging to those in industry and clinical cancer research, with the consequence that the regulation has kept important new strategies from patients for many years and does so without significant increase in protection for the patient. At this meeting and many others, it is clear what regulatory reforms are needed. The first and perhaps most important is to decentralize the IND process. This is an activity introduced into regulation with two major purposes: the first is to regulate the academic community, and second is to make sure that unproven remedies that might be harmful would not be systematically investigated in patients. But since these regulations for the IND process were put into place, we have had federal legislation mandating institutional review boards and peer review in the scientific community. As a result, the necessary regulation is clearly in place in all of the academic centers. Because a major portion of the drug delay is involved in the IND process, decentralizing this activity from the federal level to the academic medical centers would greatly enhance the life of the clinical investigator. Other suggestions that have been made include using more innovation in Phase I, II, and III designs. Other reforms to the regulatory process that could greatly reduce cost, increase the speed of clinical research, and reduce the hassle factor for the clinical investigators have been widely published (23).

Summary

The bridge to the next millennium requires a strong clinical research infrastructure. This infrastructure must be built by attracting the brightest and the most energetic physician-scientists to the field of clinical cancer research. This is the bridge that will ensure an ever-improving perspective for cancer control, which is, after all, one of the major purposes of medical research and the delivery of health care to our community.

References


Fig. 4 Health care costs as a percentage of United States GDP. The health care industry now accounts for almost 13% of the GDP.
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