Cancer Research and the Scientific Community

The scientists should design and integrate the major programs of cancer research.

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The expression of governmental intent to increase the application of national resources to the study and control of disease must be considered as encouraging to the development of medical science. In this spirit, therefore, the introduction in the Senate of the Conquest of Cancer Bill by former Senator Ralph Yarborough (D–Tex.) in December 1970 and the emphasis given to the increased financial support to cancer research by President Nixon in his State of the Union message and in more recent statements should be welcomed by the entire scientific community. This is true even if we are very much concerned about the specific manner in which these resources will be used. For example, the proposal to merge the National Cancer Institute in a National Cancer Authority separated administratively from the National Institutes of Health has led the discussion into a much-publicized battle over a single administrative form. The reporting of this matter has done nothing at this time to clarify the need for improvements in the organization of cancer research, a need which in fact led the consultants to the Yarborough committee to their legislative proposal. Nor does this discussion seem to point to the real need for more funds in this area and how they should be spent. Nevertheless, it is already clear that more money will become available to medical science; a healthy ferment has been stirred in the National Institutes of Health and the scientific community generally, and opportunities for proposal, counterproposal, and new directions have become available.

At this point I will take the position that I really do not care whether the financial and administrative support given to cancer research is mediated through a National Institutes of Health or a National Cancer Authority, if it can be shown that the form is best adapted to the needs of the problems and does not distort our national needs in other medical and scientific areas. However, it should be clear that I do not consider that the present forms have provided the intellectual and monetary support currently needed. Furthermore, I do not see how an appropriate administrative form can in fact be chosen in the absence of well-defined goals, programs, and priorities. It is precisely for this reason that the scientists must get into the act and must participate at every stage in order to facilitate the development of a suitable administrative form. If we do not participate in this chore, our programs and priorities will be set, as they have been in the past, by the administrators who are already fighting for the power and the bodies, which include us.

The scientists seem at the present time unable to describe their needs in an integrated and effective way. Probably few among them have seriously thought of the various needs of a set of problems which range from the nature of a cancer cell to treating malignant disease in a complex patient. Furthermore, it may well be that fundamental information may not be sufficient for the development of a detailed program of experiments and priorities. Nevertheless, many of my colleagues are certain, as a result of startling progress in cell biology in the recent past, that we are on the verge of important advances. Therefore, at the least, we must affirm the sense of excitement and promise with which new resources will be greeted. Also we should attempt to assess our scientific position as a step in the effective use of the material opportunities that are promised. It is one of the purposes of this article to ask the scientists (i) to join the discussion, (ii) to inform the public, the legislators, and the administrators of the important opportunities afforded by the past three decades of growth of biological science, and (iii) to determine how to integrate our efforts to solve problems. I have several suggestions concerning the last objectives, which seem somewhat unreasonably to conjure visions of 1984 to many of my colleagues. However, the major point of this article, perhaps, is to indicate the nature of our present disarray.

Within this context we may ask if the current discussions of these problems in *Science* and *Nature* have been helpful. Staff reporters in both journals have failed to provide a serious analysis of the development and deficiencies of the varied structures within which cancer research takes place. Both journals have stressed the battle between the forces eager to administer the proposed expanded funding. The journals have neglected the scientists, who must make the discoveries that will be possible only when they are given the necessary resources. The public, which supplies the patients (one in four) that make this enterprise so urgent, is never mentioned. If one is to read the article by R. J. Bazell [*Science* **171**, 877 (1971)] the concept of improving cancer research as developed by the consultants to the Yarborough committee, is a "disease" spread by "conspirators," whose leader is a Madame Roland type, adept in "both familiar and novel political maneuvers" which have been used to engineer "the establishment of a commission, filled with friendly faces." Despite the fear of being hoodwinked, which is engendered by this article, I must shamefacedly admit that I share the point of view of this hardworking, public-spirited body of consultants who have said that cancer is important and that we must improve our approaches to dealing with it.

It is my opinion that, although we are far from understanding in detail all the major scientific features of our problems, a major impediment to the solution or solutions of cancer lies in the organization of science itself. This suggests that, unless serious changes are made in this organization, research progress in this field will be unnecessarily slow and inadequate. In speaking of "the organization of science," I am referring to the entire complex of

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educational institutions, cancer institutes, industrial organizations, and government and private funding agencies involved in cancer research in the United States. I will endeavor to indicate that we do need a more appropriate national scientific organization with ample funds and administrative support that can define critical research areas on a short- and long-term basis and point to a stepwise solution of these defined problems. It will be stated that existing organizations have in fact failed to cope with the historic, scientific, and administrative exigencies of the special basic and clinical problems in clarifying and handling cancer. A survey of our present shortcomings and opportunities is presented below.

Recent History of Medical Advance

Chemotherapy and the magic bullet. The dramatic discovery in the late 1930's and the 1940's of effective chemotherapy for many bacterial diseases by sulfa drugs and antibiotics led to the hope that virus diseases and cancer might be conquered similarly in the not too distant future. However, it became clear by the mid-1950's that the biochemical bases of antibiotic action on bacteria, rather than on the hosts they infect, reside in the special qualities of structure and function of bacteria with respect to cell walls, membranes, and ribosomes. The biochemical differences among virus-infected cells, tumor cells, and normal cells are far more subtle; although there are differences, they are more difficult to establish and to exploit by chemical inhibitors. We are now in a position to approach these problems more realistically.

Making better rifles and bullets. The observation that antibacterial agents were not useful against viruses and tumors led to more sophisticated efforts to design compounds against these entities. An empirical methodology designed to discover antibiotics for bacteria was adapted to the detection of natural or synthetic compounds that could act against viruses, virus-infected cells, and tumor cells. Simultaneously, an improved knowledge of cellular and virus structure and function also facilitated the design of possible chemical inhibitors. Despite much serious effort, chemical inhibitors so detected have been found to be inactive or only partially effective against tumors in animals or in man. However the results have not been wholly negative, and indeed about a dozen agents have been significantly helpful for certain types of tumors and sufficiently promising to warrant continuing work. Some of these compounds have been nucleic acid analogs, and these have found their way into a therapeutic armamentarium. We are left with the following major problems: Why are partly effective compounds not more effective, and how can we make partially effective compounds more efficacious?

Our knowledge of the target. For many reasons, the major advances in our knowledge of cellular biology after World War II began in virology and bacteriology. The fruits of these disciplines in the 1960's have been the development of molecular genetics and great progress in the clarification of cellular growth and multiplication in microorganisms and in higher cells. Cellular biology is a sophisticated discipline, as well as the center of much experimental work and progress. Since cancer is a disease beginning with the transformation and development of individual cells, we have only recently attained the ability to explore the origin, development, and cure of cancer in a scientific way.

The foregoing sections state, therefore, that:

1) Hopeful misconceptions concerning the efficacy of empirically detected antibiotics have been eliminated and clarified in the past 20 years.

2) Promising leads for therapeutic agents exist but have been revealed to be far from perfect or even adequate in the treatment of cancer.

3) For the first time scientific progress in cellular biology has made the study of cancer and cancer cells an appropriate subject of detailed analysis.

Organization of Cancer Research

Universities after World War II. The great increase of medical scientists doing research in medical schools after the World War II was in most instances an unplanned phenomenon. In addition to the expansion of personnel into individual departments on so-called hard money, there was a new soft money contingent of workers funded by the new types of research support that developed in the 1950's. In very few instances did such expansions consist of integrated efforts in cell biology, although occasional departments active in cancer research, such as those at the University of Wisconsin and Yale University, were organized. In the immediate postwar period, the principles underlying the acceptance of individuals into biological research in universities were personal creativity, and minimum cost to the university in funds, space, and equipment. It is clear, therefore, that the selection of medical scientists tended to concentrate work on small problems that did not involve collaborative work or extensive facilities.

Furthermore, since cellular biology is a relatively new discipline, studies within this discipline in medical schools were effected within essentially all preclinical departments, with the possible exception of organ-oriented departments such as physiology departments or many pharmacology departments. Thus in any single school, cellular biology has been a fragmented discipline studied in many departments, with resulting duplication of efforts, personnel, equipment, and facilities. Despite this duplication, in most schools the centuries-old departmental organization has prevented the integrated teaching of cellular biology, which we have defined as the core of the fundamental aspects of cancer research. Also, even fewer schools have learned how to merge the frequently numerous fragments of strength in cancer research within the school into a curriculum of instruction on cancer, a curriculum which spans both fundamental and clinical knowledge.

Briefly then, cancer as a problem in cellular biology, which spans many preclinical and clinical departments, lacks scientific and administrative interest and centralization in most universities and medical schools. These institutions rest on traditions of scholarship, faculty promotion, and support of research which in fact pulverize efforts toward collaborative work in cell biology and human biology. As now constituted and organized, they are not suitable instruments for the development of cancer research or even for instruction in cancer biology. Although cancer research permeates medical schools, very few medical schools have attempted to integrate their efforts in oncology.

Cancer institutes. There are numerous private and governmental institutes whose ostensible aims are to perform research on cancer. Coming into existence or expanding largely after World War II, when much less was known about cancer, virology, or cell biology, the institutes rarely had systematic programs. They stressed

that, since cancer was a largely unknown entity, any research on growth would help to clarify the cancer problem. This position was emphasized to attract scientists mostly interested in biological problems other than that of cancer and to facilitate obtaining financial support for these workers. As a result, cancer institutes now contain many investigators who are only secondarily interested in cancer. The institutes have frequently obtained associations with universities and have used similar tenure regulations, which now handicap reorganization of these institutes. It is clear that, even as in the universities, research in these institutes is fragmented and lacks a serious program and direction.

I do not feel qualified to discuss the National Cancer Institute (NCI) and the National Institutes of Health (NIH). The former has emerged as the major funding unit in government support of cancer research. It would be instructive to know how much work directly related to cancer is undertaken in the NIH outside of the NCI and the extent and nature of the integration of efforts among the various institutes in this area. It is probable that the threat thought to be posed to the NIH by the Yarborough bill has compelled extensive discussion of this matter within the NIH. The results of such discussions within the NIH should be made known to the scientists, who may have some constructive ideas of their own. The relation of the research actually carried out within the NCI to the nature of the financial support given to cancer research also warrants a great deal of discussion.

The NIH has undoubtedly noted that the increasing bypass of a critical peer review system of grant funding by the NCI in favor of a less well monitored contract system has considerably disturbed some of their panelists and much of the scientific community. This subject also should be discussed openly, or scientists will view it as increasing evidence of an administrative rather than a scientific determination of research goals and priorities.

Pharmaceutical companies. In theory these companies are efficiently integrated, compentent aggregates of all the skills necessary to solve major biological problems. Such skills have been applied to the discovery, test, and development of numerous antibiotics which can kill pathogenic microorganisms (or arrest their development) in man. However, cancer does not provide a financial incentive for a large-scale attack by such companies, which have just barely begun to make serious advances in the study of virus disease. In my limited view, the lack of a critical mass of excellent biologists and biochemists in any one company and the lack of a scientifically knowledgeable administrative core have all helped to prevent such companies from effecting more than serious screening operations.

American Cancer Society. This Society, whose science advisers give considerable time and effort to the screening of proposals for cancer research, does not usually identify critical problems and attempt to obtain work to solve such problems. However, the Society does not, in principle, deny an obligation to identify and attack scientific problems, and it has established its Council for Analysis and Protection, which may develop such activities. Nevertheless, despite the numerous achievements of the Society in education and mobilization of public support, this basic weakness, as well as the relative dearth of funds, prevents the Society from approaching rapid solutions of various cancer problems.

A Proposal

I think that the work of the National Foundation for Infantile Paralysis in the identification and solution of specific critical problems may present a useful model for activity which should be adopted by the American Cancer Society and possibly by the entire cancer research enterprise. The Foundation set up a kind of general staff of distinguished scientists, who determined the state of the problems of poliomyelitis and how these might be approached. It should be noted that although poliomyelitis has been virtually eliminated in the United States, in large part through the efforts of the Foundation, all of the scientific problems connected with the disease have not been solved.

In the period of my contact with the Foundation between 1940 and 1955, the scientific general staff pointed to a need for chemists, virologists, and immunologists, and developed fellowship programs to that end. Among many other programs, they recommended support of work on bacteriophage and courses and symposia in virology; they also facilitated the transformation of phage workers and others into animal virologists, a movement which began in 1953. It is my belief that this record proves that a broad and continuing examination, assessment, and recommendation of research programs by a scientific general staff can be beneficial to the development of a science and need not evolve into one more stifling bureaucracy.

This group was also not above recommending support of specific work on particular problems, for example, the typing of viral strains, essential to the next practical advance. They sought capable scientists who were engaged in these activities and offered to help them to do it more completely. I do not consider such seductions to be an affront to science or to personal dignity.

Cancer problems are unquestionably more complex than the polio problem, and perhaps we will need several staffs for specific areas, such as cancer virology, chemical carcinogenesis, and chemotherapy. Perhaps we will also need a general staff to integrate these separate and overlapping efforts, but, in effect, the panels established by the NIH and the American Cancer Society now include the kinds of individuals and structure capable of providing these types of senior leadership. I wish to suggest that these panels, expanded and reorganized if necessary, should be identifying problems, suggesting programs, establishing priorities, and seeking answers, in addition to their present roles of evaluating research proposals.

Conclusion

In sum there is no organization on the national or international scene which can easily facilitate the solution of the numerous large and identifiable problems in cellular and virus biology, drug design, and clinical pharmacology as a rational exercise in scientific effort and collaboration. We are at the stage in biological science wherein the problems are ripe for the many excellent investigators now available. Nevertheless the structure and finances of science, as well as our scientific institutions and their leaders, are not geared to organized study and application to a disease which kills one of every six people in a painful and ugly way. I believe that it would be relatively easy to mobilize many outstanding biological scientists to aid in an organized attack on this group of diseases. Such an attack must be designed in large part by the scientists themselves.