

Trends in Cancer Research*

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Most presidents of this Association have on these occasions considered an aspect of cancer research in which they themselves have made notable advances. These presentations have all been valuable. In many cases announcements of important discoveries have then been made for the first time. These have been immediately communicated to the public by an alert press to which we extend our compliments and our thanks.

The members of the Association, and their guests, have felt privileged to listen. Yet some of them could understand but imperfectly. Progress in cancer research is made by specialists in many lines of endeavor. These specialists are immersed in their tasks. They use a language all their own, and they have a tendency to credit workers in other lines with more knowledge than they actually possess. Consequently these presidential addresses are for some of us just grand and for others on too high a plane—obviously, we can't all be equally versed in genetics, chemistry, physics, cytology, and clinical medicine, to mention only a few of them. No one brain can encompass the cancer field. An Aristotle would be floored.

I could try to follow suit and speak to you about the studies on epidermal carcinogenesis carried on by our small group since 1938; but something tells me that most of you would be bored. Instead, I shall try to follow the example of my respected predecessor, Dr. Aub. You will remember his eloquent address, "This Business of Cancer Research." It was a huge success and appealed to all of us. Being constituted as I am, I am unable to supply anything approaching his sparkling humor. I am advised, wisely, that anything of that kind from me would fall flat.

"Trends in Cancer Research" is a safe topic. The only danger is in frankness, and this I do not intend to avoid. My approach has been to induce the members of this Association to speak up for themselves and to bring before you their opinions. A questionnaire was sent out, with the announcement of this meeting, by our secretary, Dr.

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Hooker, who incidentally contributes more than anyone else to our Association. The thanks of all of us are due to him.

To begin with we asked our members to identify their line of principal research activity in the cancer field—genetics, biochemistry, chemotherapy, pathology, endocrinology, radiology, nutrition, or whatever it happens to be. The thought was that this would indicate their points of view of the cancer problem. Most of them stated that they were active in several fields.

Then we requested their opinion on specific questions. The report of a committee on "Fundamental Cancer Research" to the Surgeon General in 1938 constitutes a landmark, so this was taken as a good point of departure. The questions were:

1. *What are the chief achievements since 1938 in your field?*

As is to be expected, the answers covered a wide range of activity, and there was little consensus of opinion. They included:

- The development of cancer in tissue cultures.
- The introduction of single cell cultures.
- The transplantation of human cancer into other species.
- Hormone treatment of prostatic and breast cancer.
- The identification of the milk factor as a virus.
- Demonstration of transmissible cytoplasmic characters.
- Knowledge of submicroscopic structure revealed by electron microscopy.
- Advances in the study of metabolic antagonists.
- Use of radioactive carcinogens.
- Progress in the early diagnosis of human cancer by cell smears.
- Demonstration of association between excessive cigarette smoking and lung cancer.
- Large scale testing of possible chemotherapeutic compounds.
- Proof that dietary factors influence cancer production in animals.
- Elucidation of the function of mitochondria, especially in the concentration in them of certain enzymes.

Demonstration of the effect of specific genes on the control of susceptibility to tumor formation.

Demonstration of the association of specific genes with antigens controlling the transplantation of tumors.

Demonstration of the influence of hereditary factors in cancer production in animals.

The discovery that genetic changes result from the action of chemical carcinogens as well as from radiation.

The bringing of the chemotherapeutic agent more directly to bear on the cancer in human beings by intra-arterial injection.

Recognition of a qualitative difference between malignant and normal tissue.

From these and other answers one might easily get the impression that we have made great strides forward since 1938, that the goal is just around the corner. But sober thought tempers this complacent feeling of satisfaction. There have been advances. It can be said that we are coming to grips with the cancer problem. We are, however, a long, long way from solving it.

2. *What are the present trends?*

Chemotherapy was placed first by a wide margin. Also mentioned were: endocrine balance, sub-microscopic structure, antimetabolites, viruses, host-tumor relationships, and numerous other fields of endeavor. Evidently in the past 12 years it has not been discovered where the major offensive against cancer should be staged. If agreement could have been reached on the strategy likely to achieve success, generous financial support would have been forthcoming.

3. *What others seem most worthy of exploration?*

Many of the members naturally thought that their own work should be pushed, but some gave other lines of investigation including:

The mechanism of metastasis.

Blood diagnostic tests.

Inheritance of cancer in man.

Clinical experimentation on advanced cases of human cancer.

4. *Are any trends in your field being supported and over-emphasized at the expense of others apparently more fruitful?*

Most of the members avoided this question, some pleading ignorance, but the following opinions were recorded:

Too many programs. The idea is that these programs are designed to catch the dollars and are in a sense artificial.

Gross chemical and enzyme compositions of normal versus tumor tissue.

Production of tumors in animals by powerful synthetic carcinogens. There is little use in merely adding to the already long list unless the new carcinogen behaves in an especially revealing fashion. These powerful synthetic carcinogens are not the ones that cause cancer in man.

Heat coagulation of blood serum as a diagnostic test.

Animal genetics.

Many of the answers to the questionnaire were carefully prepared, and I am grateful for them. The task of writing all the letters of thanks has thus far been too great for me.

On the whole, the number of answers was disappointing. I do not think that this indicates indifference on the part of our members. None of the members of the Association belonging to Washington University answered. I mentioned this to a friend who said: "Oh, they know that you know their opinions anyway; they will be glad to answer if you want them to; shall I ask them to?"

But I do interpret this rather general failure to respond as an expression of a widespread feeling of futility. Our members have opinions, but most of them don't think that anything is to be gained by coming out with their views. The American Association for Cancer Research is, after all, the largest and most active national organization in the world devoted to cancer research. It is, in my humble opinion, an unhealthy condition for this Association to remain passive while large and powerful organizations devoted to financing cancer research decide which investigations are to be promoted by financial contributions and which are to be starved to death by lack of funds. Self-analysis and self-criticism can be helpful. However, the situation is not as serious as it might seem to be at first sight, for these organizations depend to a large extent on our members as consultants. The opinion of the Association is voiced through them. The American Association for Cancer Research does not realize its power.

Speaking now frankly, as an individual, I have certain opinions for which I take the responsibility. It seems to me that the report already alluded to by Bayne-Jones, Harrison, Little, Northrop, and Murphy to the Surgeon General in 1938 is equally valid today. As I have already admitted, the progress made since that time has been disappointing. We still await the discovery of weakness on the part of cancer cells, or of chinks in their armor through which they can be attacked. Leukemias and cancer that have spread throughout the body are as deadly today as they were in

1938. We can delay the outcome and reduce suffering to some extent, but beyond that we remain powerless. Despite many promising experiments, chiefly with animals, and promptly publicized, we repeatedly are forced to admit that the fates of thousands remain sealed.

But our approaches to the cancer problem change. We can recognize the appearance since 1938 of some definite trends of interest and of emphasis which did not come out in the answers because the questions were not adequately phrased.

The pioneer foundations are to be congratulated for their initial leadership. I have in mind the Donner Foundation, The Jane Coffin Childs Memorial Fund for Medical Research, The Anna Fuller Fund, and several others. When, however, powerful impetus was given to cancer research, first by the National Cancer Institute, and later by the rejuvenated American Cancer Society, it was perfectly clear that we were trying to advance on too narrow a front. Sciences that could bring to bear new technics and points of view on the cancer problem were not being explored, and some leaders in them—immersed in their own affairs—remained unaware of their ability to help.

It was logical to expand this front by directing attention to cancer and by encouraging investigators in many lines of research to concentrate on it. Some of these workers were surprised and pleased to learn how important in the cause of cancer their studies were regarded. It was not infrequently explained to them that, after all, no change in their researches was wanted, because they were already obtaining potentially significant data on fundamentals such as enzyme activity, the mechanism of cell division, and so on. All that was required of them was to accept more money and to work more diligently. The expansive trend was not only to utilize a wider range of technics and specialists but also to activate institutions throughout the United States, both strong and weak, willing to co-operate—in brief, it was to give opportunities to many.

This wise policy has paid dividends. Now the trend is to decrease the spread of funds far and near in order to fertilize cancer research in the sciences, and to concentrate on projects which appear to be most important and feasible, as, for example, chemotherapy and the differences between normal and malignant cells which may be expected to afford clues as to the specific vulnerability of cancer cells.

From the beginning, clinicians have been aware of their responsibilities. They have not been idle, but for years they have been handicapped by lack of financial support because principal emphasis has been given to so-called fundamental research on

animals in which controlled experiments are more feasible. Some have complained bitterly to me. They agree that this fundamental research must not be relaxed. However they enthusiastically welcome the trend to encourage clinical research designed to secure more prompt diagnosis and to utilize without delay all possible means to help patients with advanced cancer. This overdue shift of emphasis to include clinical research is an important sign of the times.

In addition to this increase in clinical research, we note, both in the clinic and the laboratory, an inclination to take more seriously the concept of the virus etiology of cancer. This trend results from several discoveries: *first*, the proof that more and more cancers in animals are caused by viruses; *second*, the clear demonstration that a virus may produce tumors in adults and an acute disease not apparently neoplastic in the young; and *third*, the visualization of an increasing number of viruses by electron microscopy. There is also the fact that the milk factor, now identified as a virus, would never have been discovered had it not been possible in mice to establish highly inbred strains. Viruses in human cancer may remain hidden because this method of identification is not possible. Hereditary factors in human cancer may also remain hidden for the same reason. In my opinion the virus theory, if substantiated as the cause of some cancers, will open the way to prevention and treatment. But I do not consider it likely that all cancers are caused by viruses.

Still another trend in cancer research is an encouraging increase in international co-operation. You will agree that there is no racial or geographic monopoly of wisdom. All can, and should, take part in this attack on a common adversary. At the Cancer Congress in 1947 in St. Louis, the International Cancer Research Commission was born. This is a landmark of consequence equal to the Report of 1938 to the Surgeon General to which I have frequently alluded. The Commission is the research arm of the International Union Against Cancer. At first it was very coldly received in this country and enthusiastically abroad. We, here, have a special responsibility in its support, because two world wars have left us the most wealthy of nations. I am happy to say that opinion is definitely veering in the United States toward the promotion of international teamwork in cancer research to the advantage of humanity everywhere. Those, who say rather truculently: "We have both the brains and the equipment, why waste time and money on outsiders?" are short-sighted isolationists.

Now let us ask ourselves some additional ques-

tions in the firm belief that our ways of doing things, in many respects excellent, can be improved.

1. *What do most of us consider the principal handicap under which we are working?*

The answer will be, I am sure: "Worry about how we can carry on from year to year." There has been some improvement, because an increasing number of grants are made for more than 1 year. Though a guarantee of continuation is often lacking, when the time comes there is a continuation; but until then the insecurity is nerve-racking. I speak feelingly, because this has happened to me, despite the fact that the National Cancer Institute continued to support my work I think longer than that of any other individual. Young investigators, fired by enthusiasm, devote themselves to a career of full time cancer research at their peril. If they stay in it a long time, and many years slip by, they may wake up to a realization of the fact that they are no longer in line for important university appointments.

The trend is unhappily not toward the endowment of cancer research. When the Rockefeller Foundation became convinced that some special division of medicine should be developed it did not follow the results-quick technic of annual grants. It provided endowment. Unhappily the interest yield on endowment has steadily decreased, yet absence of endowment for cancer research is still the principal handicap.

2. *Has it become easier to finance cancer research?*

If by this is meant temporary financing, the answer will depend upon the time the supplicant has been engaged in cancer research. If he is doing satisfactory work in some science that can conceivably contribute significantly to cancer, he has a good chance to get a start. The trend to expansion of the research front, though reduced, still operates. If he has been doing good work in cancer research for 10 years or more, it is not so easy. It is said that his university should support him, that others should be given a chance. On the whole, those whose task it is to direct cancer research laboratories are finding this task increasingly difficult. They will concur that this is a trend in the wrong direction.

3. *Has the mechanism of obtaining grants for cancer research been simplified and the delay reduced?*

The first answer is that it has become more complicated. I am sorry that I can't show you tonight samples of the application forms used in 1938 and in 1951. The first were a few sheets, the latter constitute small volumes. Stacked up they would reach to the ceiling. The first were appraised by a small group of experts, the latter by a series of

panels, or study units, including hundreds of persons. To begin with, an answer could be secured promptly by writing or telephoning to those best able to judge.

Now, with increasing complexity, the delay is frustrating. Moreover, the problem of making progress reports has not been simplified. The financing organizations ask for complete *in extenso* progress reports and a great many copies. But one wise foundation requests a report of one page, or at most two pages, and only one copy. You will agree that this is a move calculated to ease the burden on us, the investigators. It also serves to improve the quality of the report. It means that the investigators weigh very carefully every word and that the job of the recipients of the reports is simplified.

For this reason, I advocate this single sheet method of making progress reports and applications for funds. Objections will assuredly be raised by those who hate simplification and streamlining. If forced to, we might meet them half-way and urge the use of two forms: (a) a long form to be used for the first application by beginners unknown to the judges concerning whom detailed information is needed and (b) a short, single-page form for subsequent applications and reports by these beginners and for all applications and reports by experienced workers already well known to the judges.

I suggest, in the second place, that financing organizations reduce the number of experts in study units and panels by about 50 per cent. Over 100 advisors on any medical problem are too many. They get in each other's way. The present method is democratic, for it gives a large number of experts, regularly being replaced, whose opinions are valuable, a chance to express their views. But the said experts are busy people working for the love of it in the little time that they can spare. We are greatly indebted to them. It is not surprising that executive officers hesitate to bother them between meetings.

However, efficiency would be promoted without great sacrifice of democratic procedure if a few of these outstanding leaders were invited to devote a year to the job full time on salary, as was the original policy of the National Research Council. Some would accept and these could take the place of many. Please understand me. I am not advocating abandonment of an excellent system. Numerous advisors should be retained, working in their spare time, strengthened by others serving temporarily full time.

It would then be possible for the financing organizations very promptly to advise applicants

informally whether their requests for aid are likely to receive serious consideration. Time is precious. To be obliged to wait for several months expectantly for the verdict when, for some reason unknown to the applicant, it is clear to those in authority that the answer will be unfavorable is a disservice to cancer research. The application should not be declined, but the applicant should be informally advised to look elsewhere. One foundation, that I know well, operates on this basis to the satisfaction of all concerned.

I realize that I only have a short time longer during which I am privileged to speak as your President. In stating my views frankly I am talking to you as members of the American Association for Cancer Research who must make applications for grants. I am also addressing you as members of panels and study units who receive applications and make recommendations. It seems to me that serving in the latter capacity there are two duties: *first* to recommend the disbursement of funds wisely as I know that you do, and *second* to advise the adoption of changes which will make the task of yourselves and of your friends as applicants and investigators easier.

All of us probably can think of other means of simplification in addition to those already mentioned. Progress reports should not only be abbreviated, they should also be reduced to one per annum. Since it is the custom of organizations receiving applications to require information about all applications to other organizations, which they freely exchange among themselves, a single annual progress report should include all advances made by the particular investigator or group each year, irrespective of the sources of the financial aid but of course mentioning them. At one stroke this would give them a complete and integrated ac-

count of progress. It would also save the hard-pressed worker from making individual reports to each of them.

There is still another way in which the energy of the cancer investigator can be conserved so that it can better be concentrated on his work. It is by arrangement between the financing bodies to agree on the same fiscal year. At present my books have to be kept on years beginning January 1, July 1, and September 1. Please advise the elimination of this handicap.

I repeat, this Association does not realize its power to help itself and in so doing to advance cancer research.

Having in mind our primary objectives of preventing and curing cancer, a closer approach to the task is indicated. At present, financing organizations receive hundreds of applications for financial aid, and they consider them long, meticulously, and wisely. In a word, they are passive recipients. In addition, a more direct method to reach the goal is to follow the example afforded by the Office of Scientific Research and Development (OSRD) in World War II. This office decided what was wanted, selected the individuals who could help most, and urged them and their institutions to join the team. The trend I would like to see is to supplement the cultivation of individual initiative, which means so much to all of us, by promoting an organized and sustained attack on cancer. Some disbursing organizations already have directives actively to invite people to undertake investigations considered important. Perhaps they even have carefully matured plans of just how, in their judgment, cancer should be attacked. Action is urgent. A five-, or a five-and-a-half-day week is not sufficient. To lose time unnecessarily is almost criminal; cancer victims go on dying.