Cancer Research in Historical Perspective: An Autobiographical Essay

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I once asked a psychologist friend of mine why there were so few biographies of scientists and so many of artists and literary men. The explanation he gave me seemed at the time quite plausible. It went something like this. The life led by a poet, novelist, painter, or composer is likely to affect his creative work. This is why the public is interested in the man himself—whether his childhood was happy or not and whether his domestic life was stable, turbulent, or tragic. In the case of a scientist, all this is hardly relevant. Nor can one easily recognize the ethnic origin of a scientist, his place of work, or his attitude about life in the way one can refer, for instance, to someone belonging to the Dutch school of painting, the Spanish school of music, or the Russian school of literature. There is no such thing as Classical, Romantic, or Impressionist science; there is only good, mediocre, or bad science (alternatively, original research, the prosaic collection of new data, or the mere repetition of other people’s work, with minor variations).

Yet this is not the whole story. Trends in science are, in fact, greatly influenced by contemporary events in society, and there are undoubtedly fashions in scientific research, as there are in other spheres. As for the individual engaged in scientific pursuits, the limitations imposed by his surroundings—geographical, social, economic, and even political—may determine the direction in which his scientific bent can find an outlet and so decide the kind of research he is likely to undertake and, indeed, his future career. The originality of his scientific achievements depends on his own peculiar mental makeup, but the scope of his work is influenced by many other factors.

All of this certainly has relevance to my own early experiences, perhaps more so than with most of my colleagues and friends.

I left Czarist Russia in 1906 at the age of 3 because of a pogrom in Bialystock where we then lived. I settled in Belgium but left that country for England 8 years later when the German army invaded Belgium during World War I. Would I have ended up as a cancer research worker and become involved in my work on croton oil if there had been no pogrom in 1906 and no war in 1914? I very much doubt it. And yet one cannot speak here of a cause-and-effect relationship, but only of circumstances beyond one’s control leading to unforeseen eventualities.

Of course, not all events that shape one’s life are so fortuitous. In my own case the next significant event, which almost ruined my future academic career, was some well-meaning advice I received when still a schoolboy of 15. A friend of the family, an organic chemist by profession, came to visit us and out of politeness asked me what I intended to do when I left school. I told him that I had a passion for chemistry but was otherwise not very interested in my studies. “If only I could be accepted at the university, despite my poor school record, I would aim at becoming a research chemist,” I told him. He asked me how good I was at physics. “Pretty poor,” I replied. And what about mathematics? “Even worse.” He shook his head sadly and told me that, to be a good chemist, one’s physics had to be good, and that in turn required advanced mathematics. His information may have been basically sound, but it was psychologically disastrous. I took his implied advice so seriously that I gave up the idea of going in for chemistry and eventually enrolled as a medical student, a calling for which I knew in advance I had no aptitude or particular liking.

It was my good fortune that the Head of the Department of Physiology and Biochemistry at Leeds University Medical School (the late Professor H. S. Raper, known for his classic work on β oxidation of fatty acids in the body) had a more understanding attitude towards young people. It expressed itself, in my case, in a rather unusual way.

There was an end-of-term examination in physiology, and one of the questions to be answered happened to be very simple indeed. I dealt with it in a sentence or two and then wrote that there was an interesting supplementary question that could have been asked, to which I gave a long and detailed answer. The following week, Professor Raper called me into his room. I assumed that this was to reprimand me for writing in my examination paper about things that were not asked for, but this was not his intention. He explained first of all, almost apologetically, how there was a much simpler answer to my self-imposed question than the one I gave. I felt duly deflated! He then changed the subject and told me that there was a new program recently introduced at the Medical School which would permit two or three medical students (not necessarily the ones with the highest examination marks) to interrupt their medical studies for a year and work for an honors degree in physiology and biochemistry. Its purpose was to encourage them to take up research in one of the medical sciences after completing their medical training. He wanted to know whether I was interested in the program. What a question to ask me! I joined the course and, though I did not do at all brilliantly in the examination at the end of the year, I returned to my medical studies with the conviction that I would eventually end up as a research scientist. (Regarding the effectiveness...
of the program itself, of the five or six people who took the course during the 2-year period 1921 to 1922, apart from myself, two became professors of physiology and one a professor of pharmacology.)

It happened that when the time came there were no vacancies in physiology or biochemistry at Leeds, but there was a vacancy in the newly created Department of Experimental Pathology and Cancer Research. They were looking for a young physiologist to study the mechanism of skin carcinogenesis by tar painting. (I was told, incidentally, that the problem was not an easy one “since all the worthwhile experiments on the subject had already been done. . .”). In this way, I found myself after all doing the kind of thing I wanted in the first place, though not specifically in chemistry. (In later years, the chemical aspects of my work always fascinated me, though most of my attention was directed to biological aspects of carcinogenesis.)

So much for my personal life. I doubt if the real purpose of these essays is to interpret the term “autobiographical” too literally. Neither are these essays really meant to serve as an opportunity for reviewing one’s own contributions to scientific literature. Their aim, as I understand it, is to express some thoughts and ideas about the progress of science in general and cancer research in particular. So I shall have little to say about my 8 years of cancer research at Leeds, the subsequent 12 years at Oxford, the interim 2 years at the NIH in Bethesda, and the 26 years at the Weizmann Institute of Science in Israel since then. I realize, all the same, that reflections on historical developments occurring during one’s lifetime are bound to be influenced by personal experiences, however limited one’s contributions to these events may have been. To this extent the present essay must continue, in one way or another, to include some autobiographical references.

In the late 1920’s cancer research in Britain was largely thought of as a branch of pathology, and experimental cancer research was considered an esoteric offshoot of the parent subject involving some strange techniques: the use of laboratory animals, a bottle of coal tar, a Warburg apparatus, other biochemical equipment, etc., instead of the autopsy knife and microscope, of the conventional pathologist. Virchow’s tradition of “morbid anatomy” rather than Cohnheim’s “functional” approach (both emanating from 19th century Germany) dominated British pathology at that time. I remember the first meeting I attended that was devoted exclusively to the cancer problem: the Second International Cancer Congress, held in Brussels in 1936. By modern standards it was a modest affair, with less than 500 participants from a few dozen countries. Yet looking back, and checking my memory by consulting the published Proceedings (14), it was perhaps the most momentous Cancer Congress ever held. The first comprehensive reports were presented to the world about: (a) the carcinogenic properties of polycyclic aromatic hydrocarbons and many of their derivatives, (b) the induction of liver tumors by means of aminoazo compounds, and (c) the induction of mammary tumors by estrogenic compounds. Important early studies were also presented on the distribution and metabolism of carcinogens in the body and on new approaches to the statistical study of cancer in humans.

Many of us from Europe who came to the United States in the fall of 1939 to attend the forthcoming Third International Cancer Congress in Atlantic City left for home before the meeting had begun, upon hearing of the outbreak of World War II. During the ensuing years, cancer research continued sporadically in various parts of the world, even in Britain, with all its difficulties and shortages as the result of the all-out war effort. Communication with those working abroad was naturally restricted.

After the end of hostilities, International Cancer Congresses were resumed on a regular basis. These Congresses, held at approximately 4-year intervals, served for a time as convenient landmarks for taking stock of progress made over the years. Their usefulness is becoming more questionable, with the enormous increase of participants, the multiplicity of overlapping sessions and, above all, the requirement to submit abstracts of papers many months in advance, making their presentation somewhat anticlimactic. People no longer attend such Congresses to learn of the
latest advances but to meet fellow workers from other parts of the world. On one occasion, I was asked by a group of newspaper reporters to explain what new discoveries had come out of a particular Congress. I answered, rather impatiently, that discoveries were made between Congresses, not at Congresses!

At the Fourth International Cancer Congress held in St. Louis in 1947 and again at the Fifth Congress held in Paris in 1950, there was a sense of hesitancy and suspense. We were, in fact, witnessing the transition between the old, prewar pattern of cancer research and a new, more sophisticated approach that had not yet crystallized.

In my recent book on carcinogenesis (5), I drew a distinction between early and contemporary studies and discussed these in separate chapters, choosing the 1950’s as the transition period. In justification, I mentioned the fact that (a) the early work was largely devoted to indiscriminate fact finding, whereas contemporary studies are more often designed to answering specific questions; and (b) the introduction of new techniques in molecular biology, virology, immunology, etc., provided a new dimension in the design and planning of experiments in carcinogenesis. The same arguments apply, of course, to cancer research in general.

There were other changes as well which had an important impact, especially on those who entered the field in the postwar era. Many new cancer research institutes were set up all over the world; the subject was taken up more and more in medical schools; vast sums of money became available for cancer research; experts from other branches of science became interested in the cancer problem; the lone investigator was being replaced by interdisciplinary research teams; and young research workers felt more assured of adequate remuneration, security of tenure, and reasonable prospects of promotion to senior positions. One’s decision to apply for a position in cancer research was no longer necessarily motivated by an inner drive to “explore the unknown.” Cancer research had become a profession like any other. Nor was there a need any longer to keep abreast of every aspect of the cancer problem, so long as one had the required techniques at one’s fingertips to share in the interdisciplinary teamwork. In any case, the cancer literature had grown to such an extent that it became virtually impossible to cope with more than the part relating to one’s own specialty.

On the other hand, those locally in charge of research projects became more and more involved in administrative duties, preparing grant applications, writing of annual reports, committee work of various kinds at their own institutions and on behalf of national bodies, refereeing of papers submitted to journals, and serving on panels for assessing other scientist’s applications. (One sometimes feels that if a scientist is “indiscreet” enough to carry out a fine piece of research, he is at once put on enough committees to make sure that he will never do such a thing again!) Gone are the days when an investigator could devote himself wholeheartedly to his research work.

This admittedly one-sided picture, with emphasis on the “defects,” while taking the benefits for granted, is meant to portray a situation that might possibly get out of hand. The ever-increasing amount of published work, with new journals appearing every now and then to cope with it, is perhaps the least of the troubles. If one can no longer keep up with all the cancer literature (which was actually possible 30 or 40 years ago), there are at least excellent reviews published nowadays covering almost every branch of the subject. But one wonders what will happen if there is no longer time to read the pertinent reviews. Would one then have to rely on some form of computerization of the literature, with a special staff to sift the information according to requirements? The thought is frightening. Meanwhile, we seem to be heading for a “publication explosion.” (We would all be happier if there were fewer papers published, but it is always the other person’s papers that are superfluous, never one’s own!)

A more serious problem is the growing dependence of research on outside grants. In theory, any investigator is free to carry out the research that strikes his fancy; in practice, his choice is influenced by his chances of getting a grant to cover expenses. This is, in effect, direction of research by remote control. What harm is there, it may be asked, so long as the grant applications are carefully reviewed, with all kinds of controls and checks to prevent unreasonable decisions? The “harm,” as I see it, lies in the fact that the essence of basic research is “looking for the unknown” and that the unknown is not subject to planning, direction, or any other form of decision from outside. This is where basic research differs from applied or developmental research, in which the objectives and the methods of approach are clearly definable. Important discoveries in basic research often constitute a break with tradition, a denial of what was previously sacrosanct. The more profound the new discovery, the more likely it is to depart from the “accepted truth” as visualized until then and the more likely it is, therefore, to be looked upon with suspicion by the “establishment.” This may especially be the case during the planning stage (when a request for a grant is being submitted), when there is not yet enough evidence to convince the sceptics. We have all heard of cases, admittedly rare but nonetheless authentic, or research applications having been turned down or preliminary reports to journals refused publication on the grounds that the ideas were too wild, and the author subsequently being awarded the highest honors for his brilliant discovery.

No one denies that by and large grant applications are judged fairly and dispassionately by panels of experts and that the decisions reached, whether of approval or rejection, are usually sound. This is particularly true of grant applications that do not run counter to prevailing concepts. Where decisions may be faulty (through no bad intentions or incompetence on the part of the experts) is in the case of projects based on revolutionary ideas. These are the ones that may suffer through neglect. We are dealing here, of course, with unorthodox projects that require substantial financial support, without which the proposed work could not be undertaken. In cases in which the revolutionary ideas can be tested without extra assistance, the problem naturally does not apply.

There is also the opposite situation—a grant application for the most lavish financial support being all-too-favorably received when it happens to be in one of the more “fashionable” fields, and especially when submitted by a very persuasive applicant. This kind of encouragement can be
vasteful in money and manpower, divert help from others who may be sorely in need of assistance, and be counter-productive vis-à-vis government agencies which provide he funds if the highly subsidized project fails to live up to expectations.

This raises the important question of the optimal size of any particular research project, in science in general, and in cancer research in particular. There is at the one extreme he kind of research that can easily be carried out by a very small group, no more than a single investigator with a technician and perhaps one Ph.D. student. (In nonexperimental fields such as mathematics, the investigator could even dispense with any assistance, unless it involves laborious calculations, nowadays relegated to computers.) At the other extreme there is the "Manhattan project" set-up, with thousands or even tens of thousands of participants and an unlimited budget, without which the work would be impossible. How then to decide which of these two extremes, or something in between, is required to satisfy any particular research project?

The answer depends essentially on whether one is dealing with basic research, applied research, or the final stages of developmental research. In relation to the cancer problem, basic research refers to the study of fundamental principles not yet understood or even suspected; applied research refers to the systematic collection of data, involving outline screening, and using well-established techniques; and developmental research represents the crash program to reach a final objective, possible only when all the basic knowledge and most of the data from the applied research are already available.

If one were to take the original Manhattan project for the development of the atomic bomb as an example, the available basic knowledge in physics at the time of the project was already sufficiently advanced to render the final all-out effort successful. I have been assured by physicists that had it been attempted, say, during World War I, i.e., 25 years earlier when the basic knowledge was not yet available, it would not have had the slightest chance of succeeding.

In the field of cancer research, I doubt if we are even as advanced in our basic knowledge as was physics during World War I, let alone World War II. Any dream of an all-out effort for the cancer problem at the present time can therefore be dismissed as irrational.

As for applied cancer research, as exemplified by the systematic screening of substances in the environment as possible carcinogenic hazards for humans, a sizable budget and manpower are needed, though nothing comparable to the "Manhattan project" pattern. Whether such a program is justified at the present time for cancer chemotheraphy—by trial and error, without any theoretical basis or lead—is a more debatable point, to which I shall refer later.

The ideal size of setup for basic cancer research is harder to define, even in general terms, since it varies from case to case, according to the complexity of the techniques and the degree of interdisciplinary cooperation involved. It is, nevertheless, my personal experience that most projects in the realm of basic cancer research can be effectively carried out by fairly small units. Expansion beyond a certain size, while resulting in an increase in the number of publications, may lead to a falling off in inspiration and originality. Not everyone will entirely agree with this statement, and I myself admit that it is not more than a generalization, with notable exceptions. Yet the underlying principle of "optimal size" is self-evident.

No scientist has an unlimited number of worthwhile research projects in his mind and, if one were to assume for the sake of argument that a particularly gifted scientist working in cancer research had as many as a dozen good ideas, not all would be of equal value. As a rational person, he would naturally establish a list of priorities in his mind as to which should be tried first. On a very limited budget, and with a small team of helpers, he would naturally concentrate on the one or two ideas that strike him as most original and exciting. If his budget and manpower were increased, he would most likely begin work on ideas further and further down on the list. If he happened to be a very ambitious person, and particularly successful in acquiring grants, he would soon find himself extended to a degree where he no longer had time to pay sufficient attention to those ideas that were deservedly high up on his list of priorities. The danger, in short, is one of sacrificing quality for quantity. (I do not want to confuse the issue by quoting examples of some of the greatest scientific discoveries made in the past by lone investigators. The technical requirements of modern research no longer make this possible.)

I have concentrated so far on the "mechanics" of cancer research, without saying much about its contents, except for a brief reference to the subject as presented at the International Cancer Congress in 1936. How far some branches have expanded since then, others subsided, and new ones developed calls for some comment.

Carcinogenesis by chemical compounds has certainly expanded very much and has developed in various directions. A great deal is now known about the kinds of compounds capable of inducing tumors in animals; they range from such simple substances as certain inorganic salts, carbon tetrachloride, and β-naphthylamine to compounds of considerable chemical complexity, especially among the naturally occurring carcinogens such as aflatoxin and pyrrolizidine alkaloids, with polycyclic aromatic hydrocarbons, aminoazo dyes, urethan, etc., as intermediate groups. What is still surprising is that, while the range of classes of carcinogens is so wide, there is such a remarkable degree of chemical specificity within each group (2). In some cases, the mere shifting of a methyl group from one position in the molecule to another may change a potent carcinogen into an inactive one. The early attempts to correlate carcinogenic activity with certain physicochemical characteristics of compounds (12) failed to take into account the fact that such a correlation, if it existed, would be of carcinogenic potency with the properties of the effective metabolite of a compound (i.e., the proximate carcinogen) rather than with those of the parent compound. This has been corrected in more recent studies (13). Hormonal carcinogenesis blossomed for a time and then seemed to decline, though new interest in the subject is now apparent (7). Carcinogenesis by X-irradiation, especially in relation to leukemia development, has assumed a
degree of complexity and importance (9) that could hardly have been predicted at the outset.

Perhaps the most noteworthy developments in carcinogenesis have been: (a) the study of the mechanism of action of carcinogens in biological terms, with the development of the concept of separate stages during the latent period of induction (though here I am naturally biased, as I have been so closely involved in it); (b) the study of the metabolism of carcinogens and their reaction with specific components of the cell (10); and (c) the study of the mutagenic and other noncarcinogenic side effects of carcinogens.

Important contributions to carcinogenesis of a more technical nature include: (a) the transformation of normal cells into tumor cells in vitro by X-rays, chemical carcinogens, and oncogenic viruses; and (b) the introduction of electron microscopy as a morphological counterpart to biochemical studies at the subcellular level. (One should, of course, also refer to the many important advances in biochemical techniques, collectively referred to as molecular biology, which have had so important an impact on contemporary cancer research.)

The association of viruses with tumor development has been particularly dramatic (8) and has to a large extent vindicated some of the pioneers in the field (11) who believed that the role of viruses in cancer was greater than most people imagined. Progress in the field was for a time hampered by the inadequacy of appropriate techniques for the intimate study of the problem. In a more general sense, progress was held back by the tendency of virologists to depreciate the importance of chemical carcinogenesis, while those engaged in the latter branch of research tended to ignore altogether the role of viruses in cancer. This barrier has now broken down to some extent.

Among the branches of cancer research that have receded somewhat in recent years (apart from hormonal carcinogenesis, already referred to), the genetic study of spontaneous tumors in animals may be singled out. Its place seems to have been taken by the study of chemical genetics at the DNA level within the neoplastically transformed cell. In this connection, the binding of carcinogens or their metabolites with specific cell receptors, the mutagenic properties of many of these substances, and the mode of action of oncogenic viruses within the cell are thought to be interrelated according to contemporary concepts of tumor etiology.

There are at least two important aspects of carcinogenesis that are still unresolved when considered in relation to the current belief that neoplastic transformation presupposes a change in the DNA genome of the cell. One is how a sustained hormonal imbalance can lead to tumor development in an endocrine organ; and the other, how the subcutaneous implantation of a plastic or metal film, irrespective of its chemical nature, can lead to sarcoma development at the site of injection.

Though much attention continues to be paid to changes occurring in the tissues during the latent period of carcinogenesis, the situation is still fluid. To distinguish between specific preneoplastic changes and noncarcinogenic side effects is as difficult as ever.

A subject that has received much attention in recent years has been the role of immunity in cancer: (a) in the process of tumor induction; (b) in relation to therapy; and (c) in its possible use as a diagnostic tool. The evidence in support of the belief that the immunocompetence of an animal plays an important part in tumor induction is largely derived from experiments involving thymectomy, injection of antilymphocytic serum, etc., in association with standard carcinogenic treatment. From these and other approaches, the theory of "immunosurveillance" has emerged (though it is not universally accepted). The possible use of immunological methods in cancer therapy is based on the evidence of specific antigens to autochthonous tumors in animals and on the belief that immunotherapy might prove to be successful if the natural immunological reaction of the body against tumor cells could be artificially enhanced. The idea that immunological techniques might also serve as a diagnostic tool that would be effective long before a tumor could be recognized by conventional diagnostic means is likewise based on the presence of tumor antibodies and on the discovery of the relationship between fetal antigens and tumor antigens. The whole subject of the role of immunity in cancer is far too much with us at the present time for a dispassionate appraisal to be possible.

Experimental research in relation to cancer chemotherapy, which has received much attention for many years, has yielded some positive results applicable to the human disease, though with some reservations. The new drugs are very toxic, and the tumors tend ultimately to become resistant to their action. For comparison, one could refer to the progress made in the fight against bacterial infections, where the breakthrough occurred when antiseptics (which could not be administered internally) were replaced by antibiotics (which could), while the fairly toxic sulfonamides constituted an intervening stage. The present status of cancer chemotherapy might be described as having reached the "sulfonamide" stage.

The fact that some approaches to the cancer problem suddenly leap into prominence while others pass into eclipse is perhaps not as disturbing as might be supposed. Such trends are generally corrected in time and meanwhile engender great enthusiasm and an eagerness to explore the subject from every possible angle. It is only the overall importance of the work that is uncertain during the peak period of popularity.

Of far greater significance and concern is the fact that so many of those engaged in one discipline are unfamiliar with, and indeed uninterested in, other areas of research. This is of course no new phenomenon, but it tends to become more acute as the various disciplines grow in complexity. One example has already been mentioned in connection with viral versus chemical carcinogenesis, where the situation seems actually to have improved.

Clinicians have always considered, understandably enough, that the diagnosis and treatment of the disease in humans is of paramount importance, that pathology merely serves to characterize the type of tumor in question, and that experimental cancer research in animals may have little relevance to the human disease. This attitude has, in the past, created a gulf between the clinician and the researcher and has tended to delay the transmission of some
valuable discoveries from the laboratory to the clinic. One might say that the situation has actually improved of late, especially with regard to potential chemotherapeutic agents, first tested in the laboratory and soon after taken up by the clinician.

There is also the important issue of data on carcinogenicity, derived from animal tests but serving as pointers to potential hazards in man. Here the transmission of information is not so much to the clinician as to public health authorities, whose function it is to recommend appropriate legislation in order to protect the public. But this communication seems to operate in a rather uneven manner.

In the case of carcinogens with which the industrial worker comes in contact, legislation may be tardy but eventually reaches its objective. (Industry itself may have discovered that taking appropriate protective measures is less costly than paying compensation to relatives of those who succumb to the disease.)

Drugs used therapeutically and discovered to have carcinogenic side effects present a more difficult problem. Some are so valuable for the treatment of disease that their carcinogenic properties must be ignored. The most striking example is the X-ray (not a drug, but used both therapeutically for the treatment of cancer and as a diagnostic tool). Here, the danger lies in its abuse, e.g., for the treatment of ringworm in children, urticaria, and other nonneoplastic dermatological lesions. In this respect, legislation is far too lax, while many radiologists remain oblivious of the degree of danger involved.

An example of inconsistency in legislative procedures is the difference between the uncompromisingly restrictive measures adopted in the United States in connection with food additives, and the limited restrictive legislation adopted in connection with smoking. The "Delaney Clause" refers to any product that has been shown to be carcinogenic for humans or animals, and thus applies even to situations in which the human hazard may be minimal. In contrast, only a verbal statement of caution is required on every packet of cigarettes, although the death toll from lung cancer runs into the thousands per annum.

Within the area of experimental cancer research, the tendency for specialization, already mentioned, is a perpetual cause for concern lest the situation become more aggravated. Yet some concerted efforts are being made to counteract this trend. For example, at the International Agency for Research in Cancer in Lyon, France (where Dr. J. Higginson is in charge), the role of carcinogens in the environment is being investigated through a 2-fold approach: by epidemiological surveys, including the setting up of subcenters of research in those regions of the world where the organ distribution of cancer in humans is considered unusual; and by intensive laboratory research directed at those carcinogens that are suspected of being implicated in humans (1). These two approaches are closely integrated. (For the multidisciplinary "Carcinogenesis Program" at NIH, see Ref. 6.) More attempts at such dual or multiple approaches would greatly help to break down the barrier between separate disciplines and would serve as a salutary corrective of scientific isolationism.

One might end on a still more optimistic note. It is by no means rare for a particular branch of science to go through a phase of growing complexity, eventually to be resolved by the discovery of a unifying principle that renders the whole subject crystal clear. Although the cancer problem has not yet reached this stage, there are signs that it may possibly be approaching it. In striking contrast to the narrow specialization at the procedural level, we are witnessing at the same time the breaking down of a number of artificial barriers at the interpretative level.

The cause of cancer and the behavior of the cancer cell have in the past always been considered independent problems. One dealt with carcinogens, viruses, and their modes of action; the other, with the morphological features and chemical properties of the cancer cell, growth in tissue culture, and the in vivo response to tumor transplantation. Even in terms of ultimate objectives, the two were entirely different. The study of tumor causation was directed towards cancer prevention in humans, while research concerned with the nature of the tumor cell was aimed at a rational approach to cancer chemotherapy.

These two problems now seem to have become interrelated, for once one accepts the principle that neoplastic transformation by physical, chemical, or viral action involves a change in the genome of the cell, and that the altered properties of the transformed cell are determined by the newly acquired genetic information, then the distinction between the cause and the nature of neoplasia virtually disappears. All this is encouraging, if somewhat overoptimistic. Some of the "clarification" may yet prove to be illusory after all, and, in any case, there are still many unsolved problems and much to be elucidated before a final judgment can be reached.

One of the difficulties in evaluating progress is that not only the subject, but also the observer, changes with the lapse of time. It is only natural for a young scientist to view a subject with enthusiasm and eager sentiment, for the mature person to judge things more soberly and objectively, and for the old man to give way to some disillusionment. As the author of this essay, I should examine such symptoms in myself.

In a popular book on cancer (3) that I wrote 30 years ago, I said in the Preface that "there is a romance of science which stimulates the mind and satisfies the soul; it also happens to be the surest approach to one's understanding of the truth." That surely conforms to youthful enthusiasm, almost bordering on sentimentality.

Many years later, in an article I was invited to write in honor of Professor Khanolkar (4), I discussed among other things the illogicality of trying to discover a cure for cancer by the hit-and-miss method, rather than having the patience to learn more about the subtle differences between the cancer cell and the normal cell, as a guide to experimental cancer chemotherapy. I ended the article with the sentence: "In science, as in ordinary walks of life, speed is only effective when one knows in what direction to proceed." This seems to have all the earmarks of sobriety, and the caution and objectivity of the mature man.

In my very recent book Carcinogenesis as a Biological Problem (5), I ended the chapter "Modern Concepts of Tumour Aetiology and Pathogenesis" with the following paragraph:
"We find ourselves at the present time in the era of molecular biology, and we are perhaps unduly influenced by the genetic code as the dominant principle in biology. Perhaps, in a decade or two from now, the dominant principle may shift to another plane, which in turn will influence our speculations about tumour causation. A chapter on "Theories of Tumour Causation" might then relegate those based on genetic principles to the category of "outmoded theories," with a very different set of "contemporary" theories presented for serious consideration. . . ."

This may strike the readers as the sort of disillusionment characteristic of advancing age. Yet I do not feel that I have changed so much. I still experience some sense of adventure every morning when I set out to work, just as I did on the first day, close on 50 years ago, when I began my life as a scientist. Trying to discover the unknown is still exciting, even if the method may have changed over the years.

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