# RESEARCH IN PHYSIOPATHOLOGY AS BASIS OF GUIDED CHEMOTHERAPY

## *With Special Application to Cancer*

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*To My Wife*

FOREWORD

# THEORY AND FACTS

FEW OTHER PATHOLOGICAL CONDITIONS have aroused, as cancer has, the interest of so many scientific disciplines. Problems related to cancer have become of continuously increasing concern in virtually every field of medicine. In some, such as pathology, they are a major preoccupation. But in sciences other than medicine, cancer also has been receiving increased attention. One of the most urgent activities of synthetic chemistry today is the search for new compounds which might possibly be effective in the control of cancer. Physical chemistry is trying to provide new explanations about the variety of processes present in cancer. Even mathematical studies which recently have offered an interesting application of quantum theory to carcinogenesis, have found new applications in cancer.

With the rapid development of physical sciences, the medical research worker has hoped that from them might come some contribution that could help him ultimately in his difficult task. He also appears to have been anxious to take quick advantage of the progress of other disciplines for another reason, hoping that, through employing their findings and methodology, medicine in general and cancer research in particular, could be promptly changed from the empirical discipline it has been until now into a positive science. He has brought as many applications of other disciplines as possible into his study and this has led to a whole series of new methods of investigation through which interesting new information has been obtained. Yet, most of these applications have been tried chiefly because they have been at the immediate disposal of the scientist rather than because they have represented a missing link in the development of his own ideas.

The outcome has not been rewarding. Medical knowledge appears not to be sufficiently advanced to successfully utilize the avalanche of new, highly specialized information offered by the investigative methods derived

from other disciplines. Basic theoretical knowledge in medicine in general, and about cancer in particular, has not yet reached the level necessary to relate and assimilate the new data. To a large extent, basic concepts about pathogenic problems are not even formulated as yet. When the medical scientist has tried to transform the new data into effective therapeutic procedures, he has failed. And the failure has made more evident how much we need basic physiopathological knowledge before we are able to take advantage of detailed data.

Meanwhile, normal development of cancer research has been hindered, side-tracked from its logical course. While thousands of scientists with almost unlimited funds at their disposal are presently using the most advanced methods for the acquisition of details, almost no attempts are being made to resolve basic problems, although the cancer investigator is continuously obliged to realize the dearth of fundamental knowledge.

If we attempt to analyze this abnormal situation further, we can find indications that it may have its origin also in a distortion of the proper relationship between the two factors that, together, make for progress in research—ideas and experiment.

The experimental approach provides precise information about particular phenomena under defined conditions. The analytical method tries to investigate reality by recognizing the proper place of the various constituents of a whole, the parts being identified as such by the experimental findings. On the other hand, the conceptual method not only provides an inkling of what the completed whole will eventually look like, but also attempts to predict the properties and the relationship of the component parts.

In dealing with a highly refined and complicated subject, the analytical method by itself appears inadequate. For example, in atomic physics, the results of experiments are expressed by numbers giving the values of certain physical quantities that have been measured. In order to complete the analysis, we must simultaneously determine the numerical values of certain quantities defining the material bodies, the objects of the experiments. This is prohibitive so far as canonical coordinates by Heisenberg's uncertainty principles are concerned. With experimental knowledge somewhat curtailed, theory at present must attempt explanation.

In other areas as well, experiments present only limited numerical values pertaining to some physical quantities. Were we able to measure all quantities, we could analytically reconstruct the entire theme of the physical reality. However, when some quantities cannot be simultaneously deter-

mined, this direct reconstruction is not possible and experiments merely give an indirect approach to what we regard as "reality."

If the inadequacy of the analytical approach by itself is evident in the highly positive disciplines, such as in the physical sciences, it is even more so in biology. As Bohr and others have intimated, the conditions of uncertainty seem to be much more pronounced in biology than in physical science. The fact that experiments in biology give only fragmentary and unrelated results is not surprising; the need for a synthetic theoretical method in this field is clear.

In medicine, which is applied biology, the need for the conceptual approach is especially profound. It is true that this approach, as the sole approach, has shown its inherent weakness in the past. There was a time in the development of medicine when available data were so scarce and unreliable, and the need for ideas to provide some sort of guidance was so great, that the worker resorted to broad imagination, using it to replace almost entirely any other form of investigation.

Largely as a reaction to the high proportion of "speculations" prevalent in the early years, the experimental approach in medicine came to be emphasized. Claude Bernard, who almost single-handedly was responsible for this, tried to give experimentation its rightful role. However, in ensuing decades, the relationship between theory and experimentation has been progressively distorted. An unrestrained exaggeration of the role of the experiment, the erroneous view that pure facts represent the aim of research, has led to an entirely unbalanced approach. Not only have almost any data obtained by research been considered intrinsically interesting, but obtaining them has become the sole purpose of much research. In scientific papers today, experimental data must be reported as such; any allusion to theoretical meaning is considered undesirable. Generations of scientists have been schooled to believe in the intrinsic value of the experiment. As they have applied this belief to research in biology, and as they have made unlimited use of new methods taken from other disciplines with no ideological requirement for their use, we have had more and more data and fewer ideas. Today, with great astonishment, some scientists are at last beginning to recognize not only that data alone do not generate ideas, but that science cannot progress without theory.

Ideas and experiments are integral parts of all scientific research. A balance between them is needed to assure progress. It must be understood that the function of experimentation is to guide our thinking, to help build up new concepts, and to prove their accuracy in accordance with reality. Certainly, fundamental concepts must not be mere "speculations." They

should be accepted only after confirmation through experimentation. Experimentation is the necessary link between mental concept and reality. To the attempts to consider any unresolved fundamental problems in biology, one has to try to bring a rightful balance between conceptual views and experimentation.

The exaggerated importance attributed to experimentation in biological science, its use even as a substitute for ideas, has led recently to a massive attempt to solve the therapeutic problem of cancer by indiscriminate screening of chemical agents. Here, empiricism has been brought to its culmination. After tests of tens of thousands of agents, many workers are now beginning to realize that the results are almost worthless for cancer therapy in humans, that seemingly promising agents have an effectiveness limited to the conditions present in the actual animal experiments. By its impressive magnitude, the failure of indiscriminate screening, of empiricism epitomized, has begun to impel many workers to change their idea as to what must be done if the cancer problem is to be solved. A first result of this change has been a new and, this time, unbiased evaluation of just where we stand in our assault on the cancer problem. Every day more scientists are making the evaluation in their reports to the medical profession and to the public with a candidness which, only a few years ago, very few would have employed.

## The Present State of the Cancer Problem

Surgery in cancer can be considered to have arrived now at or near its maximum efficiency. Thanks to progress in operative techniques, and to advances in pre- and post-operative care, ultraradical surgery is available today. The propensity of cancer to spread far from its original site has made such surgery obligatory in many cases if there is to be an effort to eliminate all malignant cells. Yet ultraradical surgery has not sufficiently increased the cure rate to justify horrifying mutilations, especially when the face is involved. With few exceptions, surgical procedures do not prevent the patient from dying of cancer sooner or later. The so-called five-year-cure-rate represents, to say the least, an unrealistic appraisal. Many authors consider that even the rate of five-year survival is not improved by surgical procedures, and the ultimate fate of these five-year survivors, with few exceptions, is still disastrous. Most of the "cured" cases still die from cancer.

Other recently discovered facts have increased skepticism about the value of surgery in cancer. The polycentric origin of cancer, especially in

cases where the lesions are far apart—considered by some workers to be true even in malignant melanoma, for instance—would greatly limit the value of surgery as a means of eliminating all cancerous cells. It is recognized that to operate on a lymphoma is useless. Furthermore, it is known today that cancer cells are present in the circulating blood. Surgical manipulation has been found to induce a flow of these cells into the blood even from relatively small primary tumors.

In view of all this, cancer cannot be considered to be a condition for which surgery is a major hope. Surgery represents only an expedient—to be tried so long as nothing better can be offered. It is probable that in the future it will be reserved, in cancer treatment, for the correction of mechanical complications, such as intestinal or other duct occlusion.

Unfortunately, radiation has not been much more successful in its long range results. In order to control cancer, it is necessary that radiation destroy all the cancer cells present in the organism while producing minimal damage to normal tissue. It appears that such high selectivity of action cannot be obtained. The lack of it may be implicit in the nature of the effects achieved by radiation. A study of the biological effects of radiation, which is to be presented later in this monograph, has shown that an important part of the action of radiation is to induce changes in certain constituents of the body, principally fatty acids. These changes are largely responsible for the favorable effects of radiation but they also are largely responsible for the undesired effects. It is the nature of these changes which limits qualitatively the capacity of radiation to influence cancerous processes, and makes it dubious that progress in technique can ever greatly improve the qualitatively insufficient effectiveness of radiation. Clinical results to date provide confirmation of this pessimistic view. The recent use of extremely high voltage radiation, of radioactive cobalt, and of other radioactive particles has not greatly improved results over those obtained with older forms of radiation twenty years ago, except for reducing some harmful immediate skin and systemic effects. Now, as earlier, with few exceptions, the benefits of radiation are no more than temporary. Long lasting good effects still are limited to only a few radio-sensitive tumors.

The resort to isotopes, in which the scientific world has put so much hope and millions of dollars, also has proved greatly disappointing. Of the thousands of cases of various kinds of cancer in which isotope therapy has been tried, only a very limited number of cancers of the thyroid have responded. Not only because of its continuing failures, but because of its inherent qualitative inadequacy, radiation does not appear, any more than surgery, to represent the solution for the problem of cancer.

With surgery and radiation therapy incapable of resolving the problem, more and more research workers have turned their efforts in other directions. The existence of some cases of spontaneous remission has led many investigators to believe that immunological procedures related to cancer would be able to resolve these problems. Unfortunately the existing knowledge in this specific field is too meager to permit more than some tentative investigations, usually only repetitions of similar researches made many years ago with limited success. Fruitful development of this approach would have to follow the normal pathway, starting with more knowledge of the complex immunological processes intervening in cancer.

An enormous amount of cancer research in recent years has been directed toward chemotherapy. It is a fact that many agents and groups of agents have shown the capacity to influence tumor evolution. However, each has had limited usefulness. Results of treatment have been characterized by inconsistency. Even in seemingly susceptible types of cancers, results have been good in one case, poor in another and have varied even for the same patient at different times. The inability to explain and remedy these variations has discouraged many workers. Although it appears evident that the source of discrepancies resides in the patients themselves, the general tendency among researchers has been to try to resolve the problem by finding agents able to act independently of any differences which exist between subjects.

In despair at the lack of progress in this approach, many workers today are using the screening enterprise mentioned above as a kind of last resort. For this project, they have renounced the scientific concept that pharmacodynamic activity must serve as the basis on which an agent is to be tried in therapy. They have fastened into a purely empiric approach. Now, all available chemical substances—and many others which will be synthesized especially for the purpose—are to be screened indiscriminately, for their effects on animal tumors with no reason for this test other than that the agents are, or can be made, available. We will not dwell here on the assumption that routine technique is more likely than imaginative brain power to resolve the problem of cancer. The results of this screening to date have shown it to be an invalid procedure, as expected by most critical workers. With tens of thousands of substances already tested, the busy screeners are obliged to recognize that the approach itself is fundamentally erroneous. Experience has proved that an agent can be wonderfully effective against one tumor and still be entirely inactive in others. Of tens of thousands of agents tested, less than a hundred have shown effects on

tumors in animals. None appears to have significant value when applied in humans.

These results have emphasized again the importance of factors other than the agent itself. One factor lies in the differences which exist between various tumors. Some of the other factors include variations between species, between individuals of the same species, between origins of tumors, between spontaneous and transplanted tumors, and even variations in any one individual at different times.

Faced with this situation, some workers have concluded that not one treatment but at least hundreds of different treatments must be found in order to cope with the huge variety of conditions.

Taking cognizance of these considerations, it has seemed to us that a more realistic and logical approach is to try to understand the nature of the existing differences and to attempt to make the treatment adequate on the basis of that understanding. It has been this approach which has been followed in our research.

We have studied the problem of cancer for the last thirty years from an entirely different vantage point than that used by other workers. Attention has been focused on the physiopathological aspect of cancer, on the basic changes that occur in the different patients, with the ultimate aim of understanding the part played by these changes in the response of cancer to therapeutic attempts. This emphasis on the physiopathological aspect of cancer has been made possible by applying a more general overall idea of the nature of the disease.

This approach is based under various new concepts. They concern,

1) The role of the organization in the pathogenesis of the conditions.
2) A dualistic systematization of the manifestations related to normal and abnormal physiology.
3) The predominant intervention of certain constituents such as lipoids and chemical elements in the induction of the opposite manifestations.
4) The possibility to integrate the occurring processes into a system of *defense mechanism* against the noxious influence exerted by the environment.

Many general and special problems of physiopathology, some of them concerning cancer and other conditions, have been analyzed in this framework.

The application of this approach to therapy has resulted from a logical development of that approach. The recognition of the intervention of a variety of pathogenic factors, not only differing from one subject to the other, but even changing in the same subject during the evolution of the

condition has emphasized the need for individualized therapy. As opposed to the tendency to overcome the differences existing between individual subjects through a standard therapy, the "guided therapy" utilizes the knowledge of the occurring different pathogenic particularities in order to correct them. A high degree of flexibility in the treatment has appeared necessary.

As part of this approach to therapy, has appeared the need for more complete knowledge of the existing differences and their interpretation in terms of the pathogenesis of the condition. The search for adequate analytical tests has thus represented the first task. The development of day-by-day analysis of the condition has been possible by choosing relatively simple but reliable procedures. The information they offered was used to determine the nature of the agents able to correct with a certain specificity, the encountered pathological conditions. These two parts, the recognition of the existing condition and the adequate agents, have concretized this approach.

These considerations explain also why the new developed "guided therapy" cannot be understood and correctly applied without a sufficient knowledge of its physiopathological and pharmacological basis. These same considerations have led us to present the research concerning this approach as a block, instead of fragmented communications. The form of a monograph has appeared consequently the best suited. In a further effort to achieve a cohesive presentation, we have separated from the text most of the technical and experimental data, and presented them as notes at the end of the text.

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