The Paradoxical Situation in Carcinogenesis

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Optimistic Mistake or Pessimistic Truth?

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CONTENTS

LIST OF FIGURES

FOREWORD

Science is the highest manifestation of human intelligence. The development of new ideas frequently takes a dramatic form and people who devoted even a part of their life to the development of science have added their own passions and emotions to it. The most contemporary and costly equipment become completely useless items unless scientists' investigations and research are ignited by a fruitful idea, an inspiration. First the idea and then its experimental or logical justification—this is the path to be travelled by a real researcher!

Sometimes an epochal contribution to science consists of a new understanding and interpretation of a fact or event rather than in its discovery. In this case, the researcher provides new ideas and concepts to explain the empirical observations and experimental data that have been incoherent and which previously they could not make an accurate account of.

The development of science is closely interlinked with ethical problems. Who should be considered the author of a discovery, the one who first pronounced an idea and himself proved its correctness or the one who provided qualified advice and assisted the initial researcher in the work in every way? Or do both have equal rights? Does an assistant enjoy equal rights to a discovery which he made together with his teacher? Can F. Polender, a German scientist, be considered the discoverer of the causative agent of anthrax, as he was the first to discern the causative agent of the disease in his light microscope but failed to associate it with the disease and thought the discovered structures were just a lower plant? Can D. Ivanovsky, a Russian scientist, who considered the infectious agent that formed in a bacterial filter to be a small bacterium growing in an artificial nutrition medium, be considered as the discoverer of viruses? These and many other problems still remain unsolved and still present the subject at issue.

It seems that the actual discoverer of a definite object or event, in addition to seeing and recording the object or event, should also generalize its importance, guess its real essence, relate it to a definite process or disease, and find the proper place in nature for it. Only in that case should a scientist be considered as the discoverer of any event or object.

In general, when surveying different spheres of biology and medicine, certain discoveries or ideas that outstripped for decades and, sometimes, hundreds of years, the intelligence of the period, used to attract attention. For example, the ideas of Avicenna, Fracastoro, Ockhan, Jenner, Pasteur, and Hallion were indeed revolutionary for their time and therefore in most cases remained incomprehensible to their contemporaries. Thereupon, it is worth remembering the French scientist Auguste Conte, who as early as the mid-nineteenth century expressed a "blasphemous" idea, predicting the time when reproduction (ovum fertilization and division) would occur without any intervention of man! For voicing such an idea, he is mentioned in the well-known book by Cesare Lombroso *Genius and Insanity* by rather unpleasant epithets. However, by the start of the twenty-first century Conte's prediction was no longer found to be far from reality. Remember parthenogenesis and reality of this process even for mammals!

Usually, the discovery of any fact or event is necessarily preceded by the gathering of facts, the so-called ripening of human mentality and by "approaching" the problem gradually, evolutionarily. In such cases the discovery or invention stays on the agenda for quite a long time and if one researcher for any subjective or objective reason fails to grasp it, it will become the gain of another, or several researchers will, independently from one another and at about the same time, settle the problem. There are many such examples in the history of science: 1) light microscope construction and the study of different objects at the turn of the sixties and seventies of the seventeenth century (Leeuwenhoek, Hooke, Malpighi, Swammerdam, et al.); 2) discovery of bacteria at the turn of the sixties and seventies of the nineteenth century (Polender, Davaine, Pasteur, et al.); 3) discovery of viruses in the nineties of the nineteenth century (Mayer, Beijrinck, Ivanovsky, Loeffler); 4) cell theory creation in the thirties and forties of the nineteenth century (Dutrochet, Schwann, Schleiden, Virchow); 5) theory of immunity creation in the eighties of the nineteenth century (Mechnikov, Erlich); 6) discovery of artificial radiation (Roentgen, Bacquerel, Sklodowska-Curie, et al.); 7) bacteriophage discovery (Twort, d'Herelle, G. Eliava); 8) creation of a polio vaccine in the fifties of the twentieth century (Salk, Sabin); 9) discovery of immunologic tolerance in 1953 (Hasek, Medawar, et al.): 10) discovery of inverted transcriptase enzymes in 1970 (Baltimore, Temin, Mizutani); 11) cardiac allotransplantation in 1967 (Barnard, Kantrowitz); 12) HIV discovery in 1983–84 (Montagnier, Barré-Sinousi), and many others.

One very interesting and, most importantly in our opinion rather sad, circumstance should be mentioned in this connection: even leading scientists such as L. Pasteur, R. Koch, S. Ramón y Cajal, I. Beritashvili, and others used to frequently become the victims of envy, ignorance and intolerance. How many scientists, who have given mankind the greatest discoveries even at the cost of their own health and life, were undeservedly forgotten or so committed to the earth, could not even imagine that their contributions, ideas and scientific articles would be so valued by the future generations? Such unvalued geniuses were Lamarck, Oken, Servet, Semmelweis, Norton, Mendel and many others. The burial places of some of them are unknown today. On the other hand, their scientific heritage is much appreciated by grateful generations.

Any problem in science can be solved in two ways: 1) the radical, sudden solution of the problem by storming; and 2) the gradual accumulation, generalization and thorough analysis of facts. The first way is rather infrequent. It is like a beam, depending more on the revolutionary idea of a definite researcher. The other way is much more frequent and often takes many years, decades or even centuries. It may be compared to evolution. One may often hear: “the idea has matured” or the opposite: “the idea has not intellectually matured yet” or “the idea is still beyond our comprehension.”

It is well known that for developing any method of treatment, the knowledge of the cause of the disease is necessary (or desirable). If the cause is known, an effective remedy against the disease can be easily found. Medical history knows only a few cases when, despite knowing the aetiological agent, effective medications could not be developed. Such diseases include leprosy and influenza, for example. At the same time, opposite examples are also known, when the ignorance (or non-discovery) of the aetiological agent of the disease did not interfere with the development by some scientist (e.g. E. Jenner, L. Pasteur), thanks to their brilliant intuition, of an effective therapeutic or preventive agent (e.g. smallpox and rabies vaccines).

In general, the professional and objective criteria of a scientist’s success (number of publications, journal impact factor (JIF), citation index (CI), physical conditions, etc.) are sometimes not at all the measure of success.

1. Everyone knows that the absolute number of publications does not represent an objective criterion. It is quite possible that more useful information is contained in a small number rather than in a large number of publications.

2. The JIF is not an objective criterion either, primarily because some journals demand large sums for publishing an article (which a mere mortal cannot afford).

3. As regards the CI, much significance here is ascribed to the sphere where some physicians or biologists are engaged. For example, the CI of a

palaeobiologist working on fossil turtles will, naturally, be higher than that of a specialist working in the sphere of carcinogenesis. In addition, the sole work of a researcher could have particularly high citation rates. At the same time, it should be mentioned that the CI is still the most objective criterion in assessing the performance of a scientist.

To the listed criteria I would necessarily add one more and rather important, in my opinion, criterion—the one concerning a new idea! Does a scientist have any, even if false, new ideas? Otherwise the scientist would follow others' thought-out ideas or stick to the beaten track. That type of scientist only repeats the facts and ideas already acquired by other scientists. However, on the other hand, no one would challenge the necessity of conducting such kinds of research.

Thus, in our opinion, the most objective criteria in assessing a scientist are CI and the existence of a new idea. Although, for a person engaged in a completely different sphere (jurisprudence, pedagogy, engineering, etc.) the absolute number of publications of some physician or biologist, all the more the JIF, the CI, and so on, are of no special interest. What a person wants is that medicine and biology would progress so as to eventually solve the problem of influenza (which from far away, from the dilettantish standpoint, does not seem so difficult).

Great is the human race's aspiration to learn the laws and secrets of nature. At the same time, science cannot develop without contradictions. Facts and fantasy frequently come into conflict with one another. In a whole number of cases facts play the role of a so-called cold shower for a fantasy.

Hypotheses and theories are the guarantees to advance science. A hypothesis is a substantiated speculation to explain some event or process, requiring further checking and proof of facts. In other words, a hypothesis is an idea suggested as a possible explanation for a particular situation or condition, but which has not yet been proved to be correct.

Any hypothesis should interpret facts of older hypotheses and be added to new facts, or the facts that have levelled the previous hypotheses.

When can a hypothesis transform into a theory? This will occur only if it is logically reasoned and does not conflict with other gathered facts. Thus, a theory is an aggregate of ideas in the specific field of knowledge. Unlike a hypothesis, a theory should be substantiated with experimental data. New ideas should not be based only on facts. They should proceed from the recognition of some regularities and fundamentals of logic.

A certain chain reaction presumably occurs between a hypothesis and a theory: the hypothesis is followed by search and investigation that brings forth new facts. All this is a continuous chain: facts, hypotheses, theories. . . and again new facts, new hypotheses, new theories, etc.

According to some philosophers, a theory can be ascribed to a field of science only if it can be negated through an experiment. But if a theory is not negated will it forfeit its status? If a theory is true, how can it be negated? In addition, the negation of a theory, as soon as some of its postulates are negated, conflicts with the actual practice of science development. Science frequently has to retain the negated theory at least until a more successful theory is shaped. Direct examples of this are some theories dedicated to the problem of cancer. It is a well-known fact that many theories of carcinogenesis have not only retained their historical significance but are still of a certain scientific interest. For example, some postulates of R. Virchow's irritation theory are still topical (especially in the case of trauma); the Warburg's biochemical theory, which seemed to have been finally negated once, is now being reanimated by some scientists; although the principal postulates of viral-genetic, or immunological theories have been negated, their future rise is quite possible.

As it seems, theories and hypotheses are of a temporary nature and tend to frequently change in connection with the collection of facts. According to S. Ramón y Cajal, "facts remain while theories are outgoing." Theories and objective data are interconnected with close causal relationships. Theories and hypotheses are the best intellectual instruments of a scientist, which with the lapse of time might grow old, covered with rust and require some amendments to be made to them.

The human mind is somewhat conservatively tuned and has to try hard to receive a new idea, especially one proposed by another person. Therefore, any person, regardless of their IQ, still finds it hard to switch over to a new idea and part (even temporarily) with the original idea, on which they might have wasted much time; in other words, for years the person has been captivated by their idea and hardly can transfer to a new direction.

A new direction in any science, even if reflecting the reality, will soon find its principal opponents fighting it through irreconcilable polemics as well as ignoring it. The latter might appear to be an even more effective tool, since it deprives the scientist of the possibility of engaging in polemics and makes them become indifferent both toward their own self as well as toward their scientific data. The reason for such principal opposition may be the fact that a new idea (assuming it reflects the reality and naturally is well reasoned) mercilessly crushes the existing disciplines and views and makes scientists transfer to a field that is comparatively unknown to them, which is actually not easy for them.

Medical history is replete with instances when in order to realize their idea scientists had to spend time proving the idea during ardent discussions with their principal opponents. Examples of this are Pasteur, Libich, Erlich, Mechnikov and others. These great scientists gained acceptance by their contemporaries (and in general!) and the reason for this was only one: the authors of the ideas (naturally if the idea is reasonable) looked farther ahead than their opponents.

In general, the scientist should possess a wonderful talent for observation and intuition which should coincide with a deep creative ability.

A scientist should primarily convince themselves of their idea's validity, fighting concurrently their own subjectivism. This is a rather difficult task. Yet more difficult is to convince others, not only the principal opponents or simply the envious persons, but also the quasi benevolent critics.

It is often the case in science that scientists united to solve a great and rather important problem gradually switch over to studying individual small parts, completely forgetting the initial objective. Frequently, they will discover a fact which they were not looking for initially. The most graphic examples of such allegedly "accidental" discoveries are those by A. Fleming, T. Schwann, and L. Pasteur. On the other hand, such cases necessarily require a mind prepared for a discovery, or "everyone can see but few can understand what they see."

Rather frequently, discoveries take place at the boundary of different sciences. This is excellently mentioned by one of the founders of the cell theory, the German Theodor Schwann: "The major advantage of our epoch consists in the fact that individual disciplines of natural science become more and more closely linked with one another and exactly this interpenetration and replenishment condition the most important successes of natural science that have been achieved lately." These words were written about 170–175 years ago.

As early as the sixties and seventies of the twentieth century, scientists were conventionally divided into 1) true, genuine scientists; 2) organizer scientists; and 3) commercial scientists, i.e. business scientists. Regrettably, lately these have been added to, with 4) grant scientists; and 5) bluff scientists. It should be said that the last three categories are characterized by intratransitional forms and their differentiation is somewhat difficult. And finally, 6) the category of scientists we name as plagiary scientists. They have always been and will, regrettably, always be.

1. *True, genuine scientists*. Much attention is attached to the aspiration for knowledge in the history of humankind. Sometimes it is hard to even imagine that these individuals zealously strive to handle a definite problem and, in spite of numerous disappointments, do not reject sometimes abstract ideas that are completely misunderstood by the majority. For these types of people the craving for power, wealth, and glory is completely alien. They

make a precedent of honesty in society. Such people have sacrificed all to arrive at the truth: personal happiness, their own hopes, and, finally, even their own lives. Such scientists, whose number, regrettably, is being dramatically reduced, are infected with idealism. For example, when I. P. Pavlov was awarded the Nobel Prize (1903), a certain businessman tried to persuade him to invest some of the money he had received in stock exchange speculation, promising large profits. The scientist answered indignantly "I have earned this money by unceasing scientific work, and science never had, does not have, nor ever will have anything to do with the stock exchange."

2. *Organizer scientists*. The number of scientists of this type is rather large. They found research establishments and institutions, provide equipment and modern facilities, and staff these with skilled personnel.

3. *Business scientists.* For scientists of this type (if they can be named scientists) science has become one of the spheres of commerce. Such "scientists" used to be considered disreputable in the sixties and seventies of the twentieth century; as for now, they have much increased in number. These scientists write dissertations for remuneration; publish articles or monographs, where they include the personalities who do not know much about these articles or monographs and are doing it for money; they influence academic councils, research societies, and funds.

4. *Grant scientists*. The grant-based financing of science has not actually been proved to be correct. It is universally known that grant-based financing dictates that researchers follow a perfunctory approach rather than engage in in-depth studies. In addition to weak scientific work, this may find reflection in practical medicine: e.g. in exchange for definite remuneration (grants), the doctor may apply into clinical practice an unproven medicine and test it directly on the patient.

5. *Bluff scientists.* Academic data falsification is not only amoral, but also sheer nonsense: repeated experiments on the same subject will necessarily reveal falsehoods. The most illustrative example of such a scientist (a bluff-scientist) is the American medical researcher W. Summerlin. We do not think he is the only one in the list of bluff scientists.

6. *Plagiary scientists*. There were, are and will always be plagiarists. The existence of "scientists" of this type is actually the greatest problem for contemporary science.

Possibly, the great numbers of categories 3–6 "scientists" have become the cause of so many unsolved problems in biology and medicine.

INTRODUCTION

To the question asked in an international survey: “Which discovery would bring the greatest benefit, the greatest good, for mankind?” the absolute majority of the population of France, Germany, Italy, the United Kingdom, and the United States of America answered approximately so: “The cancer problem solution.”

The age of cancer is much older than the age of modern humankind—cancer existed much earlier than the origin of civilization. This disease has been constantly hanging over humankind as a sword of Damocles. In South Africa, scientists discovered the earliest known case of one of the world’s most deadly diseases. The researchers diagnosed an aggressive type of cancer called osteosarcoma in a foot bone belonging to a human relative who died between 1.6 and 1.8 million years ago. A femur (thigh bone) cancer was found in a *Pithecanthropus* on the Isle of Java that had been living there some five hundred thousand years ago. The oldest known benign growth was found in a rib of a Neanderthal, excavated in Croatia, thought to be one hundred and twenty thousand years old. Signs of osteosarcoma were found in Egypt, in the bones of a young Pharaoh, living four thousand years ago. Humeral bone cancer was described in a warrior living one thousand years ago. It is noteworthy that tumour growth (in particular, osteosarcoma) was also found in the bones of dinosaurs living on the Earth in the Age of Reptiles (from about 245 to sixty-five million years ago), long before the emergence of *Homo sapiens.*

Nobody thought that the cancer problem would shift from the twentieth century to the twenty-first century! Unfortunately, oncologic diseases have remained one of the main causes of human mortality at present (2018). This is conditioned by the circumstance that researchers are still far away from understanding tumour growth, the cancer cell essence.

Humankind has the right to be justly proud of the progress that has been achieved in fighting different serious diseases. Some diseases, such as smallpox, have been eliminated; some terrible diseases, such as anthrax and the plague or black death have been almost wiped out. The latter even threatened the existence of civilization proper during the later medieval period. Cholera and malaria seem today somewhat distant and associated with the exotic. Polio and tuberculosis have significantly lost ground. In spite of this, nature has in store for humankind many surprises (which are not always pleasant). It is sufficient to name AIDS and the Ebola virus.

It is universally known that science is frequently characterized by spiral developments. For example, the cusp of the nineteenth and twentieth centuries entered the history of medicine as a "bacteriological age." At that time, most important bacterial discoveries were made. It is exactly the period when a whole series of scientific articles concerning the isolation of bacteria from cancer tissues were published. These bacteria were supposed to initiate the malignant growth. After a long time, one might say that the hypothesis on cancer as an infectious disease of bacterial origin was discredited. It was found that the theory was incorrect and that the bacteria identified in malignant tissues which had settled in the already-formed tumours—especially in the case of necrosis—were cancer contaminants rather than its initiators. After about one hundred years (since the cusp of the twentieth and twenty-first centuries and up to now), researchers again started to seriously consider the role of bacteria, and particularly of their toxins, in the formation of cancer.

It should be generally said that cancer from every quarter is a unique disease. Any infectious disease has, as a rule, its aetiological agent, or a microorganism specific for the given disease. In such a case, the researcher's task is to find the specific substance (chemical agent or antibody), which is directed against exactly the specific microorganism. The so-called "magic bullet"—a scientific concept developed by a German Nobel laureate Paul Ehrlich—has been justified almost exactly in infectiology. As regards other anticancer preparations, their search is hampered because of some disease-related circumstances. In particular, we are still unaware of the microorganism that causes cancer in humans. On the other hand, even in the existence of such a microorganism, we will be faced with the difficulty of the circumstance that this microorganism could be only an initiator of the malignant process, while the further tumour growth could be taking place, presumably, without the participation of any aetiological agents. In other words, the fight against the microorganism (or other agent or factor) after a malignant cell has been formed will yield no real result. It is the cancer cell that has to be controlled. To do this, the essence of the malignant cell proper should be known.

Thus, cancer is also a unique disease because identifying the effective mode of its treatment requires the knowledge of not only its causative agent but also of the essence of the cancer cell proper, of its formation mechanism, as well as the development of a method of controlling the atypical cell on its basis.

The formation of a malignant cell in the organism does not mean the development of cancer, the same as bacterial entry does not mean the development of an infectious disease. To develop a malignant process, the tumour cell should initiate proliferation that is detrimental to the organism. The final stage of carcinogenesis is an independent tumour growth without participation of an aetiological agent.

Cancer is also unique in respect to the circumstance that a cancer cell (which from the standpoint of the karyogamic theory is formed as a result of fusion of two normal somatic cells and remains in a latent condition up to a definite moment) is the organism's own cell, which behaves as a hidden enemy in full compliance with the rules written by the organism. According to the first of these rules, the division of cells in an adult organism is strictly controlled and takes place in different tissues at different rates. At a given moment the cell stops obeying this rule established by the organism and starts inconsistent, i.e. uncontrollable, division. As a result, the cell transforms into a malignant cell; at that point, this property (uncontrolled cell division) is transferred to the next cell generation in succession.

The proliferation of cells is the barest necessity for an organism. Proliferation accounts for the preservation of a species, individual growth, wound healing and defence reactions taking place in the organism. On the other hand, proliferation may go beyond the factors controlled by the organism and the cells would then initiate uncontrollable tumour growth.

At present, the cancer etiopathogenesis problem is one of the most complicated and interesting in modern biology and medicine. Probably no other scientific issue has attracted such attention from researchers.

The origin of malignant tumours, their essence, is still the utmost secret that, to this day, remains undivulged. It is thought that the problem's complexity is incomprehensible to the mind of the people of today; in other words, the cancer problem supposedly exceeds the intellectual resources of modern humankind. In cancer research, there were cases when a certain researcher or a team of researchers created illusions that this centuries-old problem had been allegedly solved and that the magic key that would eventually open all the doors where the problem's secrecy is kept had been found. Unfortunately, in all such cases, in the end the researchers were bitterly disappointed. The key so hardly fought for would open at best one or two doors but fail to open others. The secrecy remained unresolved and, as can be seen, is still unresolved.

Frequently, a question asked is: is cancer a hereditary disease or not? The results of animal experiments should be treated cautiously; their direct extrapolation to humans frequently causes misunderstanding. For example, it is known that as a result of the action of the so-called Bittner virus (the "milk factor"), mice tend to develop breast cancer. The offspring of the mice diseased with mammary gland cancer were also found to become ill with the cancer of this localization. The fact allegedly evidences the hereditary nature of cancer. However, further research corroborated the fallacy of this conclusion, because the "milk factor" was not taken into account. The mice mammary gland cancer-causing virus (the same milk factor) is transferred to the offspring through the milk. The proof of this has been obtained rather easily: high-tumour-incidence young were separated from the mother mouse and fed on the milk of a low-tumour-incidence mouse strain. Under such conditions, cancer was not inherited.

As has already been mentioned, not only ancient Egyptians but also the dinosaurs of the Reptile Age suffered from cancer. In the twentieth century, cancer became one of the major causes of human mortality. In 2012, about fourteen million new cancer cases and 8.2 million lethal outcomes were registered. Supposedly, the number of new cases of illness with cancer is to increase by about 70%! This is conditioned by the following circumstances:

1. *Increase in longevity*: If previously a sufficient number of people died of infectious diseases in childhood or in middle age, they simply "failed" to get ill with cancer—presently cancer threatens a comparatively wider contingent of people. Once, many scientists shared a popular opinion that if a human had managed not to die of any other cause, they would necessarily get ill with a form of cancer. The correctness of this statement, and in such a categorical form, is naturally rather doubtful and controversial, because in case it is recognized, cancer development will be considered as the final stage of human ontogenesis. Apart from the incoherence of such a possibility, rather frequent cases of longevity also evidence against it. Can it be claimed that hundred-year-old long-livers fail to achieve the final stage of their life?

It should also be mentioned here that old age is one of the major factors of cancer development. Cancer incidence dramatically grows with age. It seems the phenomenon, in addition to age, is taking place in parallel with the accumulation in tissues of various risk factors (e.g., chromosomal aberrations, precancerous cells).

2. There is no doubt that one of the causes of the increase in cases of cancer would be a *significant improvement of diagnostics.*

3. The numbers of people in contact with various carcinogenic agents and factors in the environment and/or in their workplace based on specifics of their work (so-called occupational cancer) have significantly increased in number.

4. In addition, as compared with distant ancestors, we lead more "dangerous" lives in terms of oncology. In particular, the world around us

is polluted with carcinogens and we do everything to worsen the situation. Therefore, the lately observable regrettable tendency of cancer incidences can also be explained by the dramatic deterioration of the ecological situation, nuclear power plant accidents (e.g., Chernobyl), overdose of nitrogen fertilizers, and many other factors.

Thus, if cancer cases became more frequent, blame should fall on the human race. Earlier, only small professional teams had contact with carcinogenic substances, in particular, chimney sweeps, aniline colour manufacturers, uranium and copper miners, and asbestos production workers. Today, carcinogenic agents and factors pose a hazard at a global scale. For example, the concentration of benzopyrene in large cities tends to increase from the emissions of industrial plants and automobile exhaust gases. For detailed information around the subject refer to Chapter 11 “Cancer Control Measures.”

A definite predetermined and unaltered level of cancer morbidity presumably exists for an individual society. In any specific period, individual cancer cases will necessarily amount to a definite general number. If, owing to some reason, oncological diseases are observed less frequently in males than in females, then, according to this hypothesis, the predetermined level would be still preserved because the number of diseased women would increase; where the incidence of breast cancers is low, then based on the above regularity, the balance will be necessarily maintained—the carcinoma of uterus tubes or skin will rise in frequency; the incidence of kidney cancer might cause a reduction in the incidence of liver, brain or thyroid gland cancer, etc.

All this is a hypothesis that has its followers and opponents. It should be mentioned here that the fallacy of the hypothesis becomes evident if we recollect the strange increase in the cases of lung cancer in England, accompanied with a decrease in the incidence of other cancer forms. Another example is the cancer incidence rate in Japan for the period of the country’s industrial development.

Has the sphere of oncology become for some researchers an end in itself, an intellectual pastime? Rather frequently, multiplication of sufficiently known individual details of search and retrieval takes place. And these details do not facilitate at all the generation of new ideas, the creation of new generalizations. Sometimes, the impression is given that such researchers do not bother much with the final results. And really, we see that the absolute majority of the currently published articles and monographs are dedicated to a rather specific sphere of oncology or to unimportant already-known details. This gives the impression that the modern scientific idea is sunk in meaningless empiricism in the realm of oncology. At the same time, rather seldom are general biological ideas on the problems of carcinogenesis seen, while there are few discussions around this rather important issue.

Are the sums allocated for cancer control always properly spent? This issue is not really one to be decided and discussed by us. However, some relevant facts need to be mentioned—Charles B. Huggins, who in 1966 was awarded the Nobel Prize for his discoveries concerning hormonal treatment of prostatic cancer, received two million dollars (USD) over fifteen years from the American Cancer Society as subsidies, while Denis Burkitt started his very significant scientific activity subsidized with only fifteen pounds (GDP), to be added to with another one hundred and fifty pounds after two years that were spent on the purchase of an old car necessary for distant trips. Such things are not rare in science! This is further evidence of the difficulty, frequently the impossibility, of perceiving the actual value of this or that line of scientific activity.

As stated by the well-known French scientist G. Mathé "The major part of funds spent on nucleic acids failed to extend the life of one cancer patient even for a day." According to some scientists, nobody doubts that if the cancer problem ever managed to mobilize the same personnel and the same funds as during the making of the atomic bomb, progress would be quickly achieved. Is it so? The problem will be discussed in more detail a little later!

Generally, it should be said that much funding has been invested into cancer control research, and concurrently, less thought and analysis. Money has great power, but the fact that it cannot solve everything is certainly beyond doubt. Money is, regrettably, a precondition for bringing to the forefront the so-called business scientists, administrators of all kinds. This fact being very good for them, their interests are rather bad for research and researchers. Scientific and research empires have been established and there is nothing good in that. No good will or, as can be seen, has come out of it. In the investors' opinion: "Since we have invested so many millions into research, be so kind as to give us the outcomes corresponding to these millions." They do not understand and are not eager to understand what science is and that the planning of real science, its shaping into certain forms, is nonsense.

As far back as 1964, a Virus Cancer Programme was created to function over fourteen years. The major objective of this programme consisted of identification of the viral aetiology of human tumour diseases, as well as studying viral carcinogenesis mechanisms.

In 1966, the report of the National Advisory Cancer Council (NACC) stated: "The possibility that the cause of leukaemia is a virus is so great that the National Cancer Institute in subsidizing scientific articles pays a special attention to this specific problem and hopes that the leukaemia stamping out will be possible by the vaccine like in the case of poliomyelitis." At the same time, in a statement by the US Department of Health and Human Services (HHS) it was said: "Based on the present-day level of knowledge, it can be determined when a successful completion of special scientific research concerning leukaemia will be possible."

In the sixties and seventies of the twentieth century, numerous attempts to infect experimental animals (mice, rats, hamsters, monkeys) with the blood and other tissues of a human ill with leukaemia were made. Yes, such attempts were many in the world, especially in the former Soviet Union, where several groups composed of highly skilled specialists were working on the problem almost concurrently. All expected the outcomes of these experiments with great optimism. The successful completion of such experiments would evidence the viral origin of leukaemia.

Unfortunately, said scientists (including all oncology researchers) were to face great disappointment and gradually their enthusiasm has significantly slowed down in that direction. The disease invoked in the experimental animals turned out to be a leukemoid reaction rather than the true leukaemia. The virus-like particles identified in the bone marrow and blood of the infected animals, as a result of a scrupulous ultrastructure analysis, turned out to be elementary mycoplasma particles. At the same time, the following question remained unanswered: what was taking place upon infection of the experimental animals (naturally, in the case of a positive result)—the transfer of human leukaemia virus to animals or the activation in the animals of the latent virus under the impact of the human blood or bone marrow?

The hopes of scientists for developing a universal cancer vaccine are great (although certain researchers predict the development of such a vaccine only after several decades). The year 2018 nears its end and the hullabaloo around the viral origin of cancer is gradually reducing. Hence, the reader should consider whether the funds spent on the cancer problem are always properly allocated. And not only the funds! The incorrect idea might lead to the waste of valuable time, even decades!

The anticancer vaccine should neutralize the bulk of not only the virus causing the cancer and leukaemia (although these two diseases are the same problem of the same science—oncology), but also all viruses; this should take place, which is very important, before a virus invades the cell and causes its tumour conversion. Even in the case of tumour transformation of one cell only, the proliferation of morbid cellular elements might acquire a fantastic rate: for example, in the case of children's acute leukaemia, the number of tumour cells doubles every four days. It means that upon retaining such a proliferation rate, the generation of one malignant cell will reach in 164 days (approximately five months) one trillion units, equalling thus the unfortunate (lethal) outcome.

In spite of the fact that current research into the sphere of oncology is allegedly in the process of stagnation, every day we await some positive result in this sphere, but in vain! To our mind, the mass breakthroughs in medicine were possible some 75–105 years ago. Suffice to remember the discovery of compounds composed of arsenic to control *treponema*—the causative agent of syphilis by P. Ehrlich (Salvarsan 606, Neosalvarsan 914). The greatest breakthrough was the discovery of penicillin, sulfanilamide, streptomycin, etc.

Unfortunately, we cannot boast of such victories in the sphere of oncology! In the sixties of the twentieth century we learned something new about cancer cells. Every new step taken in this direction (even if very small) can be considered as the greatest achievement. All this is incomprehensible only for a person unfamiliar with the problem. At that, practically any achievement (even *ex facto* insignificant) implies the laying of the foundation stone of the building erected by scientists and nobody knows the laying of how many such foundation stones will be necessary.

The fight against cancer has turned out to be very challenging. Currently, definite stagnation is observable in the sphere of carcinogenesis. However, let us hope that this is a temporary event. An important breakthrough should necessarily take place in the near future. The research carried out in the sphere of carcinogenesis is always a gold mine of human intellectual potential.

In general, the human mind, human psychology if you like, is so arranged that it is eager to be the outright winner over this really terrible disease. It wishes that scientists would one day develop the so-called panacea (e.g. in the form of a vaccine) and rescue humankind with a wave of the hand. Unfortunately, such expectation is futile and the invention of such a panacea should not be expected soon. Nature reveals its secrets rather unwillingly. Seemingly, the human mind will cope with the cancer problem on a stage-by-stage basis, step by step, although it will necessarily overcome it in the end!

We are witnesses to the unjustified optimism which periodically captures even the leading specialists working in the sphere of carcinogenesis. They should more than others be aware of the great difficulties and disappointments a person engaged in the cancer problem (and, generally, in any sphere of science) has to face. For example, in the seventies of the twentieth century, at a joint symposium of oncologists from France and the USSR arranged at the Moscow Institute of Experimental and Clinical Oncology, the Soviet scientists were seriously trying to convince their French colleagues that the problem of cancer had been allegedly solved and that only some nuances were then being refined, for example, the development of a virus vaccine. The sceptical smiles upon the faces of French scientists and their remarks that they had already gone through such stages of euphoria several times failed to undermine the groundless optimism of the Soviet scientists. And what good did such optimism bring?

In general, optimism is a good thing and should be encouraged in everyday life. However, such an attitude (or optimism) in oncology is thought to be too early, even today (2018). When scientists listen to one another, critically overview their thoughts, not remain in captivity of their incorrect ideas, stop ignoring other researchers, misappropriating others' ideas (or any effective means against plagiarism will be invented at least!), exactly then the breakthrough in the sphere of oncology should be expected.

Chapter 1

Carcinogenic Agents and Factors

The discovery of physical and chemical carcinogens (in 1910, for the first time, a tumour was produced as a result of radiation, while in 1914 a tumour was obtained that was started with chemical substances) initiated a rather important stage of theoretical oncology development. These discoveries enabled specialists engaged in the sphere of oncology to study not only a tumour but also to observe almost all the stages of its formation and development. At the same time, studying the earlier stages of this disease became possible, which is rather important.

First of all, let us briefly touch upon the agents and factors that are presumably the causes of cancer. These are the agents and factors being diametrically different from one another by their nature; numerous physical, chemical and biological agents, the number of which is constantly increasing.

In general, it should be said that most carcinogens are man-made, especially since they have been added to with such a strong anthropogenic factor as nuclear explosions taking place in the atmosphere. The addition of a dose of ionizing radiation in this case might cause (and unfortunately has already caused!) biosphere damage, as well as a significant increase in the incidence of cancer and genetic diseases.

1. The first information about the carcinogenicity of physical factors appeared in 1910 (J. Clunet). First of all, some major sources of radiation of different natures should be mentioned: uranium, X-rays, etc. The appearance in the body of radioactive isotopes can also facilitate the formation of a cancer cell. Rather dangerous in terms of oncology are strontium-90, caesium-137, rubidium-109, carbon-14, phosphorus-32, and iodine-131, which are produced as a result of nuclear explosions and exist quite a long time (the half-lives of some elements are several decades). Mention should be made of the alpha-active isotope plutonium-239, which was found to be oncologically very dangerous when in the body with food and water. The greater the amount of said isotope in the body, the higher the incidence of tumours and the shorter the latent period of their development.

In the past, the contrast medium *Territrast* was used for X-ray examination (fluoroscopy). Only twenty years after its application, it was found that the medium could cause the development of tumours of the liver, kidneys and cancers of other localizations.

In 1983, it was opined that neighbouring cells were prone to fusion by electromagnetic waves and to result first in precancerous and then cancer cells (Kuppers and Zimmerman 1983).

The cases of childhood cancer were registered under the action of weak electromagnetic waves generated near electricity cables or power lines—television, refrigerators, computers, mobile phones, etc. (Hecht 1987).

As well as artificial radioactivity, natural radioactivity also exists: sun insolation, active cosmic rays, ultraviolet rays, heavy gas radon, some rocks (e.g. granite), etc. For more detail on the carcinogenic potential of ultraviolet rays and radon refer to Chapter 11 "Prophylactic Steps against Cancer."

According to electrophysiology data, rather high electricity can be developed in an organism itself, by which the muscle and nerve irritation can be carried out. Thus, electric pulses of a defined range and strength can be spontaneously developed in the body (e.g. during distress), which may cause perforation of the plasma membranes of somatic cells with resultant dramatic events at a cellular level (for details refer to Chapter 4 "Quintessence of Karyogamic Theory").

It is an established fact that especially dangerous in terms of carcinogenicity are the low and medium doses of ionizing radiation (and not only of radiation!). Not uncommon are the cases when high irradiation doses fail to produce the expected effect in terms of oncology, which might be associated with the destruction of precancerous cells especially sensitive to radiation, with their necrobiosis.

In connection with the use of artificial radiation, it would not be out of place to remember a letter by A. Einstein written some seventy-five years ago, where he warned everyone about the greatest danger of nuclear explosions. Thereafter with a similar protest appeared the well-known nuclear physicist F. Joliot-Curie "We should not allow that men destroyed themselves by using the forces of nature that they have discovered and overridden." As regards the discovery, here F. Joliot-Curie is completely right, while regarding the overriding—see the nuclear holocaust taking place in Chernobyl.

It should be said here that the most dramatic episodes in the history of medicine took place in radiation impact cases. Suffice to cite as examples are the atomic bombings of the Hiroshima and Nagasaki cities in Japan and the Chernobyl atomic power station accident.

Dependence of different pathological processes on rates and intensity is particularly manifested by the example of radiation of different natures. The study of the immediate and distant results of the explosions that took place in Hiroshima and Nagasaki made it possible to conclude on the greatest role of rates in the origin of the so-called radiation sicknesses, leukaemia, compact tissue tumours, genetic diseases, etc. In Hiroshima at the time (1945), over one hundred thousand out of four hundred and fifty thousand townsfolk died upon the explosion, in the explosion epicentre. Within 650 metres from the explosion, the radiation dose equalled 88.1 grays (or 10,000 roentgens), within one kilometre 17.6 grays (2,000 roentgens), within 1.8 km 0.3 grays (35 roentgens), and within 2.7 km only 0.1 grays (or 2 roentgens). What happened to the people that were within a four-kilometre zone from the explosion epicentre? Those who happened to be within the one kilometre zone of the explosion epicentre died in terrible torture several days later. Only a few of them lived up to two weeks. Those that happened to be at home during the explosion developed the symptoms of acute radiation sickness after twelve to fourteen days, as a result of which they died after several days. It should be mentioned here that according to its symptom complex/syndrome and haematological picture, acute radiation sickness is very close, or may be similar, to radiation-acquired immunodeficiency syndrome. Out of the contingent that had been exposed to radiation of about 0.5–1.5 grays, a significant number developed leukaemia, thyroid and lung cancers. It should be mentioned that the limit of these doses causing leukaemia and compact tissue tumours is very small. The tumours of the above-mentioned localizations were later added to with stomach and oesophageal cancers and lymphosarcomas. About half of the people within the two-kilometre zone from the explosion epicentre survived. Only a temporary deterioration of leukocytes, in particular the number of lymphocytes, was generally observed in the survivors. All those having survived this catastrophe (in spite of their distance from the epicentre) were subjected to such future threats as early death, cataracts, impotence, alopecia, development of tumours and leukaemia (naturally with a longer latent period). Regrettably, such a fate awaits their descendants as well.

The full scale of the tragedy taking place at the Chernobyl atomic power station reached our consciousness rather late. Numerous facts had been criminally hushed up, and it was only in 1990 that Russian scientists managed to call the tragedy the greatest catastrophe in the life history of humankind. The energy emitted as a result of the catastrophe exceeded the power of the bombs that exploded in Hiroshima and Nagasaki by several thousands. If we take the tragedy taking place in these towns of Japan as a model, it is difficult to imagine what trends are awaiting us in the near future. Especially as the Chernobyl atomic power station is still active. It should be mentioned that most radioactive elements have half-lives which significantly exceed the age of human life. This implies that no sharp reduction of their activity should be expected should carcinogenic chemical agents enter the body.

2. The first information about the carcinogenicity of chemical agents was provided by an English surgeon Sir Percival Pott as early as 1775. He observed an unusually high incidence of skin cancer on the scrotums of men working as chimney sweeps in London. He also discovered coal soot in the sores and eventually concluded that men routinely exposed to soot were at a high risk for scrotal cancer. Pott's report was the first in which an environmental factor was identified as a cancer-causing agent. The disease became known as chimney sweeps' cancer, and Pott's work laid the foundation for occupational medicine and measures to prevent work-related diseases. Researchers familiar with Pott's works for many years tried without success to cause tumours in animals by different chemical agents. Only in 1914, one hundred and thirty-nine years later, did Japanese scientists Yamagiwa and Ichikawa succeed in inducing cancer in rabbits by lubricating the skin of rabbits ears with coal tar daily for about ten months.

Over fifteen hundred chemical carcinogens are known today. As a result of the synthesis of new substances, the number of such carcinogens is constantly increasing.

The most known among the carcinogens are the polycyclic aromatic hydrocarbons (PAHs): benz[a]anthracene, benzo[*a*]pyrene (BaP), methylcholanthrene, and also aromatic aminoazo compounds, lead, arsenic, asbestos, etc. The carcinogenicity of chromium, beryllium and cadmium has been proven both under experimental conditions and as a result of epidemiological research.

A great role in the development of cancer is also given to pesticides (insecticides, fungicides, herbicides). A direct correlation has been established between the application of pesticides and the incidence of cancer in the population. In more detail the mentioned subject is discussed in Chapter 11 "Prophylactic Steps against Cancer."

As regards to nicotine, it can be said that tobacco smokers are voluntary participants of the greatest oncological experiment. Studies carried out in the USA showed that mortality from lung cancer was ten times higher in smokers compared with non-smokers. Similar results were obtained in England.