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DISCUSSIONS

Response to the Letter of Prof. L. M. Berstein

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I am grateful to Prof. L. M. Berstein for his benevolent comments and criticism. Now, concerning each of the notes:

1. I absolutely agree that the work under discussion is far from being the first and unique considering cancer as a general biological regularity. My article lacks a historical excursus in the topic because the journal frames require the maximum concentration on the subject chosen and restrict the possibility of extended comparisons. Moreover, it seems to me that the authors of the known hypotheses mentioned in the review (V. V. Khudolei and A. P. Kozlov) in their theories are based on quite different prerequisites than mine. This does not concern the recently published book by V. N. Manskikh, who adheres to approximately the same views as I on the evolutionary predestination of cancer. But unfortunately, I did not know his views when I was writing the article.

2. Concerning the *de novo* cancer. As a result of analysis of clinical and pathoanatomical data, K. M. Pozharisski comes to the conclusion that the term "precancer" is used too widely and thinks that ideas on multistage changes in the cell properties at the cancer emergence are insufficiently reasonable. I think, that for the last 16 years many changes occurred, and some subjects disputable earlier are not such nowadays. In any case, I have not seen a work considering one of the main ideas of basic oncology about the multistage character of carcinogenesis as questionable. In this relation, it is rather demonstrative that last year an Editorial Note in the *British Journal of Cancer* [1] specially marked the 50th anniversary of "one of classic" works, which was the first to coherently formulate this concept [2]. As an acknowledgment of the incessant significance of this paper, it was reprinted in the same issue as the Editor-in-Chief's Note. It is another matter that genotypic changes and their phenotypic manifestations not always can be correlated unambiguously. This has been done most clearly on the model of colorectal cancer [3]. In other cases, the picture is more ambiguous because of a sophisticated combination of genetic defects potentially leading to the same malignancies. Moreover, in some cases, early genetic changes can even not manifest themselves phenotypically (e.g., data on large "cancerization fields" surrounding the tumor focus and consisting of cells with genetic defects not detectable by routine diagnostic methods [4]).

3. Certainly, the presented mathematical model of accumulation of mutant cells in an exponentially growing cell population simplifies real events (in particular, does not take into account the effect of apoptosis) and is designed to describe the process only in general, with a particular emphasis of its features, which I think to be principal: (i) the involvement in carcinogenesis (except specially mentioned situations) of large cell bulks; in this case, the concept of a "tumor as a local manifestation of the generalized mutagenesis" is fundamentally opposed to the widely distributed opinion about the "locality" of the process; (ii) the ability of the cancer cell to be a "sensor" of mutagenesis.

This seems to be a background for the influence of the factors that are noted by the reviewer (individual and tissue-specific risk factors, ethnic and geographical variations in the incidence of the same oncological diseases). An idea came to me that mutagenesis in the different tissues of the organism is similar to sprinters' race by parallel paths. Everybody is running, but the speeds are different due to many varied causes outlined in the review. Therefore, different "runners" finish the first in different rounds. If the leader's speed decreases, another runner becomes the first (abstinence from smoking in some countries resulted in decrease in lung cancer, which was a leader during the previous years, making the first place vacant). Another example of the same type is presented by a striking difference in the structure of oncological morbidity in the Japanese living in their native land and USA (where their customs and habits are very different). The likening to runners is complicated by different "path lengths" in the case of mutagenesis: the retina cell trans-

formation needs only two mutations, whereas the same effect in the prostate needs from nine to twelve mutations. But the speeds of the cell "runs" are also different. The combination of these two factors (the run speed and path length) multiplied by many other agents influencing the process results in a very variegated picture. Thus, each tissue seems to have its own mutational "pyramid", but for me it was important to emphasize the features of the process, which are common in all cases. And the reviewer's impression that I have put the equality mark between all somatic cells in their potential of producing tumors means that I have failed to clearly express my idea.

4. As to the risk of cancer emergence in old age (the decrease in the increment intensity). It seems that a reasonable explanation of this phenomenon has been given by Steven Frank [5, 6] from the standpoint of the multistage model of carcinogenesis. If I have understood him adequately, the risk increases with age exponentially as the organism's cells pass the rate-limiting events (i.e., mutations). This is clear: the more it has been run through, the less is the number of anticancer barriers remaining ahead. This continues until the moment, when the only the last event remains, the probability of which is unchanged (it is the same in persons of both 80 and 90 years who have overcome the previous way).

5. As to using the term "gain of function" and "loss of function" applied to cancer and "age-related" diseases, respectively. Concerning cancer, no doubt, the activity of this process itself does not prevent a loss of some functions. Moreover, such losses occur nearly always and manifest themselves in the loss of some signs of differentiation. The cancer cell is literally a "werewolf", because it changes its activity vector for the opposite: the former builder of the "common home" turns into its destroyer (in this sense, the term "transformation" is adequate). "Forgetting" many of its normal functions, the cancer cell gains various functions which it had not earlier (see item 6). And the term "gain of function" has been used just in this sense. The reviewer is right when speaking about the activities of processes which underlie the pathogenesis of atherosclerosis, diabetes, and, possibly, other diseases. But I had in mind something different. Once appearing, a severe disease (infarction, insult, diabetes) is a result of the loss of functions of the corresponding organs, with no respect to causes responsible for such a loss. As distinguished from the cancer cell, the cells of a diseased heart, brain, and pancreas do nothing in addition to their normal functions (the trouble is that they cease to do what they could do earlier).

6. As to the "killer" function. This is the main point of disagreement. I think that the cancer cell's ability to kill (the manner is unimportant) is just the property which was the reason of cancer emergence as a phenomenon. Due to this property, cancer can realize a "sanitary" function of liberating the population of dangerous individuals, and this is its evolutionary excuse.

Opponents argue: there is no reason to invent anything if everything is clear. Namely, due to many stochastic causes the cell loses its "brakes" which inhibit proliferation, becomes autonomous, remembers its unicellular "instincts" (unrestrained division and migration), and this is quite sufficient to explain the further events. All occurs by itself. The cancer cell has no "purpose" to kill anybody, hence, it has no special provisions: it kills just by its very existence, metastasizing into different organs and spoiling their functions. Thus, there is no evolutionary excuse of the phenomenon.

I am an opponent of the "stochastic" model for the following reasons.

a) According to this model, the number of reasons of oncological patients' lethal outcomes is equal to the number of malignancies (which is about a hundred), and in every case, the functional failure of the organ damaged by the tumor (or metastasis) is fatal. Thus, local manifestations of the process are ruinous. In other words, a patient with the stomach cancer dies because of digestion failure, a patient with a focus in the lung dies because of pulmonary insufficiency, and a patient with the kidney tumor dies as a result of uremia.

This idea seems unsound to me. We know that one lung (and a part of the other), the whole stomach, up to two-thirds of the liver can be removed in humans (and in experimental animals for which all reasons retain their validities) without life-incompatible consequences. On the other hand, it is unclear which vitally important functions are suffering in the case of melanoma, bone tissue sarcoma, damage to sex-related organs, and lipo- and myosarcomas. In particular, patients with prostate cancer very often have metastases in the bones. What causes the death of these patients?

Clinicians know the situation of a "silent" tumor, when on the background of oncological clinical picture no primary focus can be detected (in other words, general signs of a tumor are present in the absence of local ones). The same is indicated by a frequently observed in oncological patients loss of the body weight long before the diagnosis, i.e., when no local tumor signs are present and will be absent still for a long time. Paraneoplastic syndromes undoubtedly prove the tumor ability to influence the body distantly and totally, and not only locally. Do they not confirm the "special" abilities of tumor? I think that just the existence of oncology as a special medical discipline indicates the generality of all oncological diseases, notwithstanding their type and location (not only the mechanism of emergence but also clinical signs are common). In the opposite case, the stomach cancer should be assigned to gastroenterology and melanoma to dermatology.

b) Cachexia is a distinct manifestation of the pure killer function as it is. It is a striking example of the distant and generalized influence of the cancer cell on the body, an example of its gaining special, early unusual functions. The mechanism of realization of cachexia is

more or less interpreted; it involves various agents identified already [7, 8]. And if I see it necessary to introduce a new term ("killer function"), it is only because cachexia is responsible for the death of a relatively small fraction (~20%) of the patients. I have introduced this term as a generalizing one and including cachexia as a particular case. Other paraneoplastic syndromes, as judged from the literature, do not lead to fatal consequences, although indicate "special facilities" of the cancer cell.

c) The evolutionary conservatism of cancer unambiguously proves its "necessity", the serving a real demand. The transformational resistance of different cells and tissues is finely adapted to conditions of their existence in order to prevent in any case the exception of this phenomenon from the life of a species; although for evolution (which can do everything) it would be an easy task (a slightly increased transformational resistance of the organism's cells could "force out" cancer from the life limits of the organism, if this phenomenon had even a minute negative influence on the species' viability). But this does not occur.

d) I think that data of population genetics about an inverse dependence between the allele penetrance and its incidence in the population are a decisive evidence of the "sanitary" function of cancer [9]. An emergence of germinal mutations (which hides the maximum threat for the population's gene pool) is associated with the maximum risk of cancer and, as a result, the appropriate alleles are eradicated from the population (carriers of such alleles have virtually no chance for survival).

7. I agree with the reviewer that all these theoretical arguments cannot cast doubt on practical therapeutic and preventive measures designed to prolong the patients' life. Moreover, I agree with the author of the article "Why we're losing the war on cancer (and how to win it)" [10] that to begin fighting the tumor when it has already emerged is as late as to begin fighting paralysis after insult has occurred. As in the case of cardiovascular diseases, the fight has to be performed on the "distant approaches", i.e., attempting to slow down the mutational "pyramid" growth and, thus, force out cancer from the human life limits.

In conclusion, I would like to say that the determination of my article as a *speculative* hypothesis does not seem justified to me (although it is the Editor's matter to place papers in any section, but I do not agree with this definition). Moreover, I do not consider it as a hypothesis. A hypothesis has to propose predictions, which can be confirmed or disproved in the future. But the "predictions" of the article under discussion concerning the strong influence of cancer on the genetic structure of the population and elimination of mutant alleles from the population genofond really are not predictions: they are facts known well and for long. Therefore, I think that any unprejudiced person will inevitably come to the same conclusions in response to the question "What is cancer?"

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The Closing Remark

L. M. Berstein

I am grateful to Prof. A. V. Lichtenstein for his informative response to my comments.

As it not seldom occurs, on termination of any discussion, every its participant keeps the adherence to his positions, or, at least, most of them (and this is not bad).

The explanations made still clearer the deliberated emphasizing the processes and ideas, which the Author recognizes as the most important (however, if one agrees that the cancer phenomenon has emerged for the "sanitary" function and is governed from "above", i.e., evolutionary, neither prevention program will be a serious chance of success). On the other hand, it seems useful to meditate once more upon existence of practical possibilities (if the evolution, using the Author's wording, "desire to force out" cancer from the organism's life limits (or even without its "desire")) to increase the transformational resistance of the organism's cells.

In total, the publication under discussion undoubtedly allows us to consider the problem otherwise and will be useful to readers of the Journal, and the agreement, or the disagreement with some or other its interpretations or positions only additionally makes any of us "stand still, look around...".