ISSN 0006-2979, Biochemistry (Moscow), 2006, Vol. 71, No. 8, pp. 925-926. © Pleiades Publishing, Inc., 2006.
Original Russian Text © L. M. Berstein, 2006, published in Biokhimiya, 2006, Vol. 71, No. 8, pp. 1140-1141.

DISCUSSIONS

Letter to the Editorial Board of *Biochemistry (Moscow)*

L. M. Berstein

Laboratory of Oncoendocrinology, Petrov Institute of Oncology, Pesochny-2, ul. Leningradskaya 68, 197758 St. Petersburg, Russia; fax: (812) 596-8947; E-mail: levmb@endocrin.spb.ru

DOI: 10.1134/S0006297906080153

The article by Prof. A. V. Lichtenstein, a well known researcher in cancer biochemistry, published recently in the Journal [1], attracts attention for several reasons. It seems strange, but, first of all, I would like to begin from the form, which in this case is inseparably connected with the essence. The article title is interesting, it is interestingly and unbrokenly written, and it is terminated with an extremely impressive (also in the educational aspect) list of references; very few Russian publications in basic oncology can boast such a list. And to the point, it is a pity that *Biochemistry (Moscow)* uses a "closed" (incomplete) system of citation: no doubt, the effect of the work would be still stronger if the bibliography included titles of the papers mentioned.

As to the matter and the general impression produced by it, the publication of this article in the section of "Speculative Hypotheses" (which is in itself courageous and rare for periodical editions) seems reasonable, because just such materials evoke a natural and rather fast response. What seems to be positive? Lichtenstein's work continues the line in the consideration of cancer as a general biological regularity associated with evolution. In the Russian literature, this problem has been paid attention, in particular, by V. V. Khudolei [2], A. P. Kozlov [3], and V. N. Manskikh [4] in a recent monograph. But A. V. Lichtenstein, with "evolution in mind", goes further and sees his task in presenting cancer as an evolutionary based altruistic program (which is somewhat close to the ideas of Academician V. P. Skulachev upon phenoptosis [5]), which has come into existence for maintaining the genetic stability of a population. And the current concepts are presented about the transformational resistance and Peto paradox, tumor as an "organ", and the organism's inner milieu as a source of mutagenic influences which are, at least, not weaker than the environment. Finally, based in addition on the concept of L. A. Loeb [6] and his predecessors upon the "mutator phenotype", the reader has been brought to the main, and undoubtedly, original conclusion: cancer is a local manifestation of the generalized mutagenesis coupled, as a result, with acquisition by tumor cells of the killer function, the reasons and mechanisms of which are far of being clear. But just here questions begin which make a reader reread the article once more and pay attention to the following.

1. The author admits a traditional succession of events (hyperplasia, metaplasia, dysplasia), and in some or other way associates it with a long-term accumulation of mutations and the image of a "mushroom" which has a "stem" (the process) and a "cap" (the product), but ignores the idea of a possibility of the *de novo* development of cancer – see, for instance, the works by K. M. Pozharisski and the discussion associated with them [7].

2. The author describes the mutational "pyramid" and the cell on its apex as a "sensor" which characterizes the strength or intensity of mutagenesis in the organism and the tumor as a manifestation of "mutagenesis which has occupied the whole organism" (p. 1061). It seems that here the author puts the equality sign between all somatic cells (and tissues) conformably to the potential possibility of tumor development in them. But what to do with the concepts about individual (and often tissue-specific) risk factors and ethnic/geographical differences in the incidence of the same oncological diseases? Or does the rate of accumulation of mutations in these populations (notwithstanding the leading role of endogenous causes – see above) vary with age? – however, this is possible.

3. If the accumulation of mutations with age is an established reality (and this is believed by many researchers) and this has, early or late, manifest itself as a "vapor exhaust from under the cover", i.e., a development of the tumor possessing the killer function, how to explain that in the age over 80 the incidence of neoplasm formation decreases representing the so-called "cancer incidence turnover" [8]?

4. It is not quite clear why the author considers diabetes and cardiovascular diseases as a result of the loss of function and cancer as a gain of it. But is it necessary to

hold such a contrapositive? Here the discussion of the problem could be much more protracted, but it will suffice to say that genetic factors (including the accumulation of mutations) are now thought to play an essential role in the genesis of both atherosclerosis and type II diabetes mellitus [9], whereas cancer as a biological process often exemplifies also the loss of function (see, for instance, the works by Fel' [10]). Finally, one should not forget that cardiovascular diseases, diabetes, and malignant neoplasms of hormone-dependent tissues are the main noninfectious (chronic) diseases, which have many common features in pathogenesis during the preclinical stage of the predisposition development for the disease [11, 12].

5. It is unclear why the metastasizing, anorexia-cachexia, remote "shots" of paraneoplastic syndrome type, etc. enlisted in the article seem to be insufficient for explanation of causes and mechanisms of the killer function of cancer and tumor cells. From clinical positions, just these factors are leading in the death of oncological patients. Therefore, nowadays one can read in increasing frequency that to prolong the life span of the patients (forgetting the "altruistic function of tumor", although it can appear reasonable from the standpoint of general biology), it is necessary, concurrently with the specific treatment, to take precautions against the dissemination of transformed cells, loss of appetite–body weight (not seldom caused by production of cytokines by the tumor), tumorous "intoxication", etc.

Not considering other sides of the problem, I would like, in conclusion, to once more emphasize that the article by A. V. Lichtenstein provokes true interest and stimulates further studies concerning the nature of malignancies, causes and mechanisms of their origin, and place in diseases of humans and animals.

REFERENCES

1. Lichtenstein, A. V. (2005) *Biochemistry (Moscow)*, **70**, 1055-1065.
2. Khudolei, V. V. (1992) *Vopr. Onkol.*, **38**, 1345-1355.
3. Kozlov, A. P. (1996) *Med. Hypotheses*, **47**, 336.
4. Manskikh, V. N. (2004) *Essays on Evolutionary Oncology* (Perelmuter, V. M., ed.) [in Russian], Siberian State Medical University, Tomsk.
5. Skulachev, V. P. (1999) *Biochemistry (Moscow)*, **64**, 1418-1426.
6. Loeb, L. A. (2001) *Cancer Res.*, **61**, 3230-3239.
7. Pozharisski, K. M. (1989) *Current Concepts about Precancer*, in *General Oncology* (Napalkov, N. P., ed.) [in Russian], Meditsina, Leningrad, pp. 193-213.
8. Pompei, F., and Wilson, R. (2001) *Hum. Ecol. Factors Assessment*, **7**, 1619-1650.
9. Andreassi, M. G., and Botto, N. (2003) *Trends Cardiovasc. Med.*, **13**, 270-275.
10. Fel', V. Ya. (1990) *Tsitologiya*, **32**, 407-421.
11. Dilman, V. M. (1987) *Four Models of Medicine* [in Russian], Meditsina, Leningrad.
12. Berstein, L. M. (2004) *Oncoendocrinology: Traditions, the Present, and Prospects* [in Russian], Nauka, St. Petersburg.