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DISCUSSIONS

Letter to *Biochemistry* (Moscow)

In the abstract to the review "Molecular mechanisms of mutual effects of the pathological processes during combination of diabetes mellitus and cancer. Scientific and clinical aspects" [1], Ya. A. Alexandrovsky wrote: "... the effort was undertaken to explain both detrimental and stimulating effects of diabetes mellitus on cancer". Nevertheless, the first phrase of the paper itself "Diabetes mellitus inhibits neoplasms and growth of many malignant tumors" as well as the following conclusion (p. 1613) "Diabetes mellitus prevents oncological diseases and exerts a suppressive effect on the process of malignant proliferation" and also the whole subsequent consideration determine the clear position of the author on this problem. The author's remarks on the "contradiction" of some data supported by citation of logician and mathematician K. Godel do not disprove such conclusion. As Ya. A. Alexandrovsky writes in his paper, he has proposed a "working hypothesis" which may be shortly summarized in the following form. Hyperglycemia activates protein kinase C and neutrophils. This is accompanied by myeloperoxidase release into blood stream, increased oxidation of acetoacetate yielding ketoaldehyde, methylglyoxal. The latter possesses mutagenic properties, which may underline inhibition of proliferation (pp. 1620-1621). Based on this principal consideration Alexandrovsky comes to the conclusion that diabetes mellitus antagonizes malignant growth.

I am deliberately not going to question the biochemical aspect of this hypothesis and its essence. However, in accordance with the title of that paper, I would like to attract reader's attention to the following points.

– According to modern notions, diabetes mellitus is often considered as a risk factor rather than an inhibitor of such malignant tumors as liver, colon, endometrium, and breast cancers. This together with the sequence of events (diabetes mellitus is usually diagnosed before cancer) could be particularly proved by "application" of materials of Swedish registers for diabetes mellitus and cancer [2, 3]. This can also be explained in terms of indications by V. M. Dilman [4], who considered some age-related hormonal-metabolic changes as united preconditions for the development of the main non-infectious illness in man. Impaired carbohydrate tolerance and insulin resistance are the biochemical and pathophysiological backbone for these preconditions. In fact, this circumstance does not abolish the fact that the presence of neoplastic process sometimes may promote decreased tolerance to glucose. However, this cannot be used as evidence for an "antitumor role" of diabetes mellitus.

– Experimental (e.g., alloxan) diabetes mellitus in animals is not equivalent to diabetes mellitus type 2 (which we usually consider) in man. The former is characterized by total (*absolute*) insulin insufficiency, whereas the latter represents the process characterized by a long-term stage of *relative* insulin insufficiency, which may have periods of compensatory hyperinsulinism and insulin resistance [5].

– This and other reasons argue that carcinogenesis/tumor growth in animals with experimental diabetes mellitus does not entirely reflect the problem of "diabetes mellitus and cancer" in man. When such distinguished expert as Vladimir S. Shapot [6] said about the tumor as glucose scavenger or pump he meant first of all either the experimental tumors or large connective tissue mesenchymal (but not epithelial) tumors which may possess such characteristic feature.

– The neoplastic transformation (the tumor process) is not equivalent to proliferation [7, 8] even if we put the adjective "malignant" in front of it [1].

– Appearance of a tumor (especially applicable to the problem of diabetes mellitus and many other moments) is not equivalent to its progression: risk and anti-risk factors for these two processes may not necessarily coincide.

– Hyperglycemia is not equivalent (even with some limitations) to diabetes mellitus, especially if we are talking about artificial creation of exceptionally high glucose concentration for short-term treatment of malignant tumors.

– There are some incorrectly written terms, including description of solid tumor (pp. 1612-1613), adenocarcinoma of rat mammary glands (p. 1613), MCF-7 (p. 1617), and insulin injections (p. 1620). It is possible that these shortcomings originate from incorrect translations into Russian.

In conclusion I would like to stress that even talking about "contradictions" of current data available it is not enough to know that each coin has two sides. Evidently, it is important to evaluate which side is more important.

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