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DISCUSSIONS

Letter to *Biochemistry* (Moscow)

In response to the comments by Professor L. M. Bernstein on my paper "Molecular mechanisms of mutual effects of the pathological processes during combination of diabetes mellitus and cancer. Scientific and clinical aspects" [1], I should say the following.

Contradictory results often serve as the reason for polemics; they represent rather effective stimulus for reappraisal of results of one's own studies or previous notions. Usually, supporters of certain hypothesis refer to results of own studies supporting their viewpoint. If it is not possible to characterize plausible mechanism underlying the considered phenomenon, they discuss such aspects of the problem which may explain possible reasons for alternative notions or contradictory results.

Such effects were undertaken in this paper [1] to reveal and discuss molecular mechanisms of mutual effects of diabetes mellitus and cancer. In principle such analysis would provide a theoretical answer to the question "whether diabetes mellitus potentiates or attenuates malignant growth".

According to my viewpoint expressed in that paper, the answer may be found studying **common** molecular processes which are **essential** for both pathologies. Previously it was found that intracellular processes controlled by enzymes of the protein kinase C (PKC) family not only represent a basis for diabetic complications, they also control malignant growth of cells. Some authors even classify these pathologies (including insulin resistance) as "PKC syndrome" [2].

Analyzing these mechanisms [1], I proposed the **hypothesis** that change in PKC status induced by hyperglycemia or insulin resistance, which represent the most typical manifestations of diabetes mellitus, may either "compensate" or "potentiate" PKC isoenzyme dysfunction. The latter may also be influenced by carcinogenesis processes. **The resultant clinical effects of mutual effects of diabetes mellitus and cancer will depend on the degree of compensation of diabetes mellitus and also on a type and stage of the oncological disease**.

This hypothesis explains why diabetes mellitus may suppress, inhibit, or promote malignant growth.

Consequently, results of studies indicating potential role of diabetes mellitus in the development of some tumors do not contradict this hypothesis, moreover, they support it. It should be noted that in subsequent publications the same group reported reduced risk for prostate cancer in diabetic patients [3] and lack of any dependence between diabetes mellitus and ovarian cancer [4].

This is the state of art in statistical studies of clinical data. However, it should be noted that in spite of social and scientific merit and also accuracy in criteria selected these studies remain open to criticism due to a large number of factors which were not (or could not be) taken into consideration. For example, data on combined cases of diabetes mellitus and breast [5] or endometrial [6] cancer significantly changed after introduction of body mass index (BMI) correction and diabetes mellitus remained the risk factor for these oncological diseases only in the group of obesity patients or patients with excess of body weight! For this reason, results of such epidemiological studies should be evaluated without categorical conclusions like "firmly recognized".

In animal experiments when it is possible to increase mutual effects of these pathologies (even with numerous limitations!) a completely different situation becomes clear. Experimental diabetes mellitus may not only inhibit but also suppress (not even totally!) many malignant tumors. Certain evidence exists that the more the animal organism suffers from diabetes mellitus the more suppression of carcinogenesis is observed, whereas treated experimental diabetes mellitus caused insignificant effect on carcinogenesis.

These facts may also be explained within the considered hypothesis. The thing is that diabetic complications represent a "tangle" of interrelated intra- and extracellular processes. Increased generation of methylglyoxal is one of these processes. This compound possessing a wide range of possible interactions with various molecules is characterized by potent cytostatic properties. I am not going to underestimate other possible mechanisms, but new data on relative ability of methylglyoxal to suppress malignant tumors [7] suggest that ignorance of the role and contribution of this compound into the considered processes would be a mistake.

Of course, my hypothesis should be verified, supplemented, and specified. However, it would not be expedient to follow the advice given by my opponent to a reader: "not questioning the biochemical side of the hypothe-

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sis and its essence" it is better to find only one "right" position. It is well known that radical simplifications cannot cover all varieties of forms and manifestations of the studied phenomenon. Reality is always more complex than simple schemes.

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