Discussion issues of terminology in the field of modern traditional medicine.
II. Homeopathy and ultra-low doses of biologically active substances

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SUMMARY

Issues related to such terms used in modern scientific literature as ultra-low doses, ultra-high dilutions, extremely dilute solutions of biologically active substances and their ratio with those used in homeopathy are discussed. An assumption is made about the expediency of experimental confirmation or the presence of the same regularities for the biological activity of substances in ultra-low doses, as in homeopathic preparations, or their absence.

Key words: ultra-low doses, biologically active substances,homeopathy.

RESUME

The issues related to the terms used in the literature such as the ultra low dose, ultra high dilutions, extremely diluted solutions of biologically active substances and their relation to the terms used in homeopathy are discussed. The appropriateness of experimental verification, existence or absence of similar patterns for biologically active substances in ultra-low doses and homeopathic remedies is suggested.

This article is a continuation of the discussion about controversial issues of terminology used in modern traditional medicine and in related fields, started in the previous issue of the journal "Traditional Medicine" [1]. The discussion will touch on such terms as: "ultra low doses", "ultra high dilutions", "extremely diluted solutions", which are quite intensively used recently, and not only in traditional medicine, and derivatives in the context of their relationship with homeopathic preparations from the standpoint of the characteristics of biological activity.

In domestic scientific biomedical publications, the term "ultralow doses" (SMD) of biologically active substances is most often used. The question of the correct determination of the concentration value in relation to SMD is being discussed, although already now there are certain ideas in this area. It is believed that the concentration limit for SMD is 10^{-19} M, since with it in a solution with a volume of about 1.0 ml there may not be a single molecule of the initial substance, and the entire range lies within 10^{-14}-ten-10^{-18} M [2].

The beginning of research in this direction was associated with the development of a new principle of treatment by the German physician S. Hahnemann (1755-1843) -

homeopathy. This method was based on the use of medicinal substances prepared by a series of successive dilutions (divisions) of the original medicinal substance. Physicochemical laws are strict, and according to them the number of molecules in any volume is finite and determined by Avogadro's constant, when at dilutions below 10^{24} or 10^{-24} M (in homeopathy
corresponding to potencies 24D or 12C) in a unit of volume with a high probability there is not a single molecule of the active substance. The principle of preparation of homeopathic preparations, developed by S. Hahnemann, led to the fact that the final solution did not contain the molecules of the original substance. The latter was the reason that, despite the fact that the biological effect of homeopathic remedies and their clinical efficacy has been demonstrated and confirmed quite well for almost two hundred years, the mechanism of their action is still unclear. Within the framework of this article, it would be inappropriate to discuss the correctness or lack of proof of this or that mechanism, if only because numerous disputes and debates about homeopathy arose almost two centuries ago during the life of the founder of the method of homeopathic treatment, S.

The first experimental studies in this direction were associated with the search for the mechanisms of the therapeutic action of homeopathic drugs, since their therapeutic efficacy in some diseases was so high that they competed with allopathic drugs. These studies, carried out on various biological objects, began to be carried out almost from the beginning of the therapeutic use of homeopathic preparations, and the aspects of studying the physicochemical properties of high potencies were not left aside. The review, which reflects the historical aspect of such studies, as well as some results, is contained in the recently published monograph [5].

In 1988, one of the most prestigious international journals "Nature" published an article by a group of biologists from different countries, headed by the head of the laboratory of immunology, allergology and inflammation of the National Research Institute of Medicine and Health of France (INSERM - Institut National de la Santé et de la Recherche Médicale) by Dr. Jacques Benveniste (1935-2004).

This article presents the results of experimental studies carried out over five years in independent laboratories in France, Canada, Israel and Italy, in which the specific activity of anti-IgE antiserum was demonstrated on a model of human polymorphonuclear basophils at its dilutions from $1x10^{2}$ up to $1x10^{120}$ in the form of degranulation of basophils [6]. Particular interest in the results of these experimental studies was due to the fact that the effect of degranulation of basophils was observed at dilutions above 10^{24}, when it is assumed that there is no longer a single antibody molecule in the solution. Another feature manifested itself in the dependence of the effect on the dilutions used: at some dilutions, the discovered effect of degranulation of basophils disappeared, while at other dilutions it reappeared, i.e. consistent highs and lows were observed that were not associated with a decrease or increase in antiserum concentration.

It can be said without exaggeration that the article published in "Nature" blew up the scientific world, although the appearance of the article in the journal itself was preceded by editorial comments, in which it was reported that there was no "physical basis" for the manifestation of the effects obtained in the studies of J. Benveniste's group. Subsequent repetition of experiments carried out in the presence of

the editor of Nature, physicist John Maddox (1925-2009) and two experts in exposing scientific fraud - chemist Walter Stewart and former magician James Randi - did not show unequivocal results, which gave reason to consider the initial results as unreliable [7].

In the academic scientific world, the reaction to the article in "Nature" was, in its essence, negative, and the scientific reputation of J. Benveniste was significantly shaken. But we must pay tribute to J. Benveniste himself as the head of research, and to J. Maddox, who published this article - despite the fact that the scientific community of that time was not ready to perceive such results, after this publication the attitude to both homeopathy itself and and to the problem of the biological action of the SMD has changed in the most dramatic way.

In subsequent years, various independent research groups in different countries tried to reproduce the results of studies obtained by J. Benveniste and colleagues, but no final confirmation of their reliability was obtained. The research groups used in their experiments the same test model of basophil degranulation that was in the group of J. Benveniste, with the only difference that histamine dilutions were used. As a result, in some cases the effect was absent [8, 9], in others, on the contrary, it was confirmed [10, 11].

It will be useful to note here that there are many publications in various journals, such as pro and contro reliability of the results of group J.Benveniste, but a definitive answer has not yet been found. Studies of the biological effect of SMD are also continuing, and this direction has gained a certain popularity, not only abroad, but also in our country [12–14]. As a result of the research carried out under the guidance of E.B. Burlakova at the Institute of Biochemical Physics of the Russian Academy of Sciences. N.M. Emmanuel (their beginning dates back to 1983), the main features of the action of biologically active substances in the MDS were determined, some of which are as follows [14]:

- non-monotonic, polymodal dose-effect relationship, when activity maxima are observed in certain dose intervals and are separated from each other by the so-called "dead zone";
- change in the sensitivity of a biological object to the action of SMD of various agents;
- dependence of the "sign" of the effect on the initial characteristics of the biological object;
- "stratification" of the properties of a biologically active substance as a decrease in its concentration, at which activity is still maintained, but side effects disappear.

Comparing results research group J. Benveniste with With the features cited above, we can note some commonality with the DMD of biologically active substances - this is a polymodal dose-effect relationship and the presence of “dead zones”. In order to make the comparison objective, it should be emphasized that the studies of J. Benveniste and his colleagues were not aimed at finding mechanisms of action, but were focused exclusively on the evidence-based aspects of the experiment (“double-blind” experiments, independent

laboratories, etc.). To be fair, it should be noted that similar polymodal dose-effect curves, as well as the presence of “dead zones” in these dependencies, were discovered in the 1920s – 1940s. in experimental studies of the biological effect of homeopathic preparations with various dilutions and on various objects.

Within the framework of the issue considered in this article, the results obtained by J. Benveniste's group are important from a methodological point of view, namely - how the breeding was prepared. In these experiments, one of the essential points was that after each dilution, the new solution was shaken thoroughly. In those cases when shaking was not performed, the previously observed effect disappeared, which was especially emphasized when describing the experimental results. The applied method of preparation of dilutions was completely analogous to the method of preparation of homeopathic preparations - potentiation or dynamization. This technique of shaking the drug base with a solvent at each stage of its dilution was developed by S. Hahnemann. Homeopaths are still quite conservative and adhere to the basic provisions of the fundamental works of S. Hahnemann, including scrupulously performing the method of preparing homeopathic preparations. Voluntarily or not,

Let us now return to the academic studies of E.B. Burlakova and her colleagues, in the published results of which, despite the clear analogy with the effect of MDS of biologically active substances and those obtained by homeopathic methods, a cardinal question is omitted, which cannot but worry any conscientious researcher - whether potentiation (dynamization) was carried out during the experiments, as in the preparation homeopathic remedies, or not? In many published articles, not only foreign but also domestic, when describing the methodological part, as a rule, it is indicated, for example, that dynamized dilutions of matrix solutions were used [15] or that aqueous solutions of a homeopathic preparation of sodium chloride prepared by Weleda were studied. [16]. Both the experiments of J. Benveniste's group and the results of later studies, in which it was statistically significant that in the absence of dynamization, the effect of the biological action disappeared [17], testifies in favor of the importance of a correct description of the method for preparing the solutions under study. Recent studies have shown changes in the physicochemical properties of a liquid during the preparation of dilutions using dynamization, which have been designated as a hydrohysteretic effect [18]. It is quite possible that these experimental studies confirmed the previously stated by G.A. Domrachev and D.A. Selivanovskii hypothesis about the existence of mechanochemical reactions of radical dissociation of water, when, under mechanical action, the energy absorbed by water is localized in the micro-scale region of liquid water [19].

In the context of all that has been said, one cannot but cite a very indicative quote from an article by L.P. Tochilkina, published in the journal "Chemical and

biological safety ":" ... after all, if scientists studying the effects of SMD, with a few exceptions, investigate, although highly diluted, but true solutions, then homeopathic practice often involves the use of highly potentiated divisions for therapeutic purposes, which are already "imaginary" solutions, that is, solutions that do not contain a single molecule of the original drug in a unit volume ”[20, p. 7]. This quote contains a very important question, since it is not clear what academic science means by the proven biological activity of substances in LMD: true solutions prepared in the usual way or "imaginary", homeopathic, when diluted with dynamization. It is possible that in this way academic science distances itself from homeopathy, justifying its point of view by the

introduction of a substance into the body in doses of 10-12- ten-13 M the cell will contain at least 1-10 molecules of this substance "and therefore the concentration of 10-12 and below [14, p. 392]. but if you follow a strict approach to terminology, at such practically difficult to define and rather theoretically predicted concentrations of a substance, the use of the term "dose" can hardly be considered appropriate, it is probably more preferable to mention high (high dilution) or "ultra high dilution", by the analogy that exists in foreign publications [21–24].

It is clear that there is a need for experimental confirmation by academic science of the presence of the same patterns for the biological activity of substances in the MD, as in homeopathic drugs, or their absence. An objective balanced assessment of homeopathy should be formed, since attempts to explain by academic science the nature of biological activity in SMD are still at the level of hypotheses and in essence do not differ from the theoretical attempts of homeopaths to substantiate their method of treatment.

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