Stages of research and application of high dilutions of substances

O.I. Epstein
(Scientific and production company "MATERIA MEDICA HOLDING", Moscow)

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OI Epstein
("Materia Medica Holding", Moscow, Russia)

SUMMARY

In the history of research and therapeutic use of "high dilutions" three stages can be conventionally distinguished: homeopathic, phenomenological and targeted.

At the first stage, “high dilutions” of drugs were tested on healthy volunteers in order to cause individual reactions, which did not allow homeopathy to be included in evidence-based medicine, which involves the treatment of the entire population of patients.

The second stage was characterized by the accumulation of data on the ability of "high dilutions" to induce a physiological response of the body, including at the molecular and cellular level.

Probably, the third stage is the stage of targeted application: the property of "high dilutions" was established - their ability to have a modifying effect on the original substance. This made it possible to take a fresh look at the problem of "high dilutions": in the process of their preparation, there is not an increase (potentiation) of the properties of the original substance, not a decrease in its concentration, but the appearance of a new quality (properties). To emphasize the role of technology in the emergence of new artificially obtained activity, the term "release activity" was proposed.

Experts of regulatory agencies (MHRA, EMA and FDA) made a conclusion about the possibility of registration of these drugs as pharmacological drugs.

Thus, "high dilutions" can cause reproducible physiological reactions, which allows them to be used as targeted drugs in evidence-based medicine, or used for individual therapy as homeopathic drugs - in order to transform the physiological response to the drug administration into an atypical (hypergic) reaction .

Keywords: homeopathy, high dilutions, ultra-low doses, homeopathic doses, release activity, release active dilutions, antibodies, targeted drugs.

RESUME

There are three stages in research and therapeutic use of "high dilutions": homeopathic, phenomenological and targetspecific.

Initially, "high dilutions" were tested in healthy volunteers to induce individual reactions, which allowed investigating related clinical signs and detecting phenotypic

markers in the respondents. Homeopathic medicine can only be indicated for patient with high individual sensitivity thereto setting homeopathy aside from evidencebased medicine intended to treat an entire patient population.

Next stage provided data accumulated mainly in the 197080s: "high dilutions" containing no molecules of the original substance can induce a physiological response of the organism on the molecularcellular level.

The third stage is the one of targeted application: in 1996 "high dilutions" were found to have a fundamental property – the ability to modify the original substance. This allowed taking a fresh eye: during "high dilutions" preparation, there is no strengthening (potentiation) of the initial substance's properties or its concentration decreasing, but the appearance of a new quality (properties). This was termed "releasedactivity" to emphasize the role of the technology in emerging of a novel artificial activity.

Experimental and clinical research resulted in a new type of targeted drugs. After scientific advisory meetings, experts at major regulatory agencies (MHRA, EMA, FDA) have agreed that such drugs can be authorized as pharmacological (nonhomeopathic) products.

Therefore, “high dilutions” can induce reproducible physiological reactions allowing their use as targeted drugs within the evidencebased medicine framework and also as homeopathic drugs for individual therapy – aimed at converting the physiological response to them into an atypical (hyperergic) reaction.

keywords:homeopathy, high dilutions, ultralow doses, homeopathic doses, released activity, released active dilutions, antibodies, targeted drugs.

The technology of multiple dilution of the initial substance, proposed approximately 230 years ago by the German physician and researcher S. Hahnemann, is traditionally perceived as a process of reducing the amount of the initial substance - up to conditional, imaginary concentrations, denoted by the terms "small or ultra-low doses", "high or ultra-high dilutions" .

In 1996, we first established that “high dilutions” differ from the original substance primarily not quantitatively, but qualitatively: they contain a modifying activity that is absent in the original substance, which we consider as technogenic, and which we will discuss below.

In this regard, we propose to divide the problem of "low doses" into two - physical and biological.

The physical one is that the technological processing of a solvent (purified water or a water-alcohol mixture) through its successive repeated dilution leads to the appearance of new physicochemical and biological properties in the solvent.

The biological problem is that biological systems respond in a special way to drugs with technogenic activity. Due to the high sensitivity of the organism to weak influences, historically, the biological properties of ultra-high dilutions were first revealed (S. Hahnemann, 1796), and then their physicochemical features.

Analysis of the results of scientific research, including our own, and the experience of homeopathy allows us to divide the body's reactions into "high dilutions" into

general - physiological and private - atypical reactions of individual sensitivity, and the history of their research and therapeutic use - into three stages:

1. Homeopathic stage marked by practical application "high dilutions" as individual therapy. From modern positions in homeopathy individual reactions to "small doses" are used; their distinguishing feature is the specific nature of the action.

2. Phenomenological stage - the period of accumulation of data on the ability "high dilutions" to have different physiological and physicochemical effects. Since the action of "low doses" is similar to the action of the original substance in a reduced form, various hypotheses have been proposed to explain how molecules of the original substance are preserved in "high dilutions".

3. Target stage - in "high dilutions" modifying properties that are absent from the original substance; it is shown that these properties are the basis of the biological action of "high dilutions". As a result, the approach to the problem has changed dramatically. The main theoretical question of this stage is how new properties that are absent in the original substance appear in “high dilutions”? The discovery of the modifying action of "high dilutions" made it possible to use them for directed (targeted) action, as is customary in modern pharmacology. The molecular mechanisms of the pharmacodynamic action of highly diluted drugs were studied and analytical methods for determining their activity were developed.

Let's dwell briefly on each of the stages.

I. HOMEOPATIC STAGE

The great German scientist S. Hahnemann, in fact, made not one, but two practically important discoveries:

1) a technology for processing the initial substance in the form successive reduction of its concentration by dilution, or trituration, leading, as it became clear relatively recently, to the appearance of new positive (technogenic) properties in highly diluted products;

2) a special case of therapeutic use of drugs in "high dilutions”, based on the use of atypical individual reactions caused by “small doses” – homeopathic therapy.

Hahnemann managed to make a therapeutic breakthrough, quite obvious for his time, which is due to the fact that for the first time in the entire period of the existence of medicine, he began to purposefully study medicinal preparations (in a highly diluted form) clinically - homeopathic proving, which, unlike modern canons, was carried out only on healthy volunteers. Clinical trials of "small doses" of various substances allowed Hahnemann to make several important observations: a) clinically significant symptoms - reactions to a certain drug appear only in individuals with high individual sensitivity to it; b) reactions to the drug are always specific and represent a reduced picture of intoxication with the same drug, but in toxic doses. In this regard, in the description of drugs,

used in homeopathy, in addition to the clinical symptoms identified during the proving, information from other sources on the toxicity of the original substance is also included; c) responders sensitive to the drug have common constitutional and personality traits and, most importantly, similar phenotypic markers of individual sensitivity.

Already on the basis of the first clinical observations, Hahnemann proposed the foundations of homeopathic therapy - the so-called principle of similarity, based on two provisions: 1) to use the clinical manifestations of individual reactions of healthy volunteers to the drug in "high dilution" as target symptoms for the use of this drug in patients; 2) prescribe highly diluted drugs to persons with high individual sensitivity to them (phenotypic determination of individual sensitivity).

Modern medicine knows several experimentally induced variants of immediate and delayed hypersensitivity reactions. Their common feature is the nonspecific (typical) nature of the response. Also typical are individual reactions observed in everyday clinical practice: for a large number of used pharmacological drugs in the presence of individual sensitivity, patients respond with hyperergic reactions in the form of anaphylactic shock or Quincke's edema. Individual allergic reactions to a huge variety of antigens are also limited to only a few types of clinical manifestations. Individual reactions to ordinary (not subjected to the procedure of repeated dilution) substances are protective; they are based on the desire of the organism to prevent full interaction with certain antigens in the presence of individual sensitivity to them. It is likely that highly diluted drugs are safer for the body, and as a result, individual reactions to them are specific.

To date, numerous studies have demonstrated the ability of "high dilutions" to cause various physiological effects, including at the molecular and cellular level; their features are established. In the 18th century, Hahnemann, of course, could not know about the molecular mechanisms of action of "high dilutions", but due to the ingenious medical observation and intuition, he was able to offer the only possible option for their time for their time - individual homeopathic therapy [1]. Homeopathy borders on art, since in order to achieve a therapeutic effect, the homeopath must not only correctly assess the symptoms of the disease, but also prescribe a homeopathic remedy to patients with high sensitivity to it.

Due to the fact that the hyperergic response is a reaction of the whole organism, homeopathic therapy is holistic in nature, which is the main

advantage of this direction.

Homeopathic therapy, which is individual and symptomatic in its essence, cannot a priori be integrated into the modern system of evidence-based medicine, which is based on two principles incompatible with homeopathy: a nosological approach to therapy, as well as confirmation of the effectiveness and safety of treatment in clinical trials on the entire population of patients with a certain disease.

Homeopathy - sparing holistic therapy - should not be opposed to modern evidence-based pathogenetic pharmacotherapy, but rationally complement it, especially in the treatment of chronic diseases.

For historical reasons, homeopathy has become isolated from modern science. Homeopaths could not know about the physiological (non-homeopathic) molecular-cellular effects of "high dilutions", and representatives of the natural sciences in most cases did not consider it possible to study "high dilutions", since they do not contain molecules of the original substance or contain them in speculatively small quantities, which means a priori are placebo. Therefore, starting from the experiments of Lily Kolisko [2], who studied the effect of "high dilutions" of various salts on plant growth, any reports of the biological effects of highly diluted preparations were in conflict with both homeopathic doctrine (the impossibility of any effect without observing the principle of similarity) and with a natural-science rational approach (the impossibility of the appearance of any effect,

II. PHENOMENOLOGICAL STAGE

The phenomenological stage of the study of "high dilutions" began, perhaps, with the "fashion" for the study of their detoxifying properties: the ability of "high dilutions" of heavy metals to reduce the consequences of their toxic action was repeatedly demonstrated [3–6]. The vast majority of cases of "non-homeopathic" studies of "high dilutions" were carried out in the 80s and 90s of the last century: data were accumulated on a fairly large number of biological or physicochemical effects of "high dilutions". Since the presence of such effects contradicts the basics of pharmacokinetics, various "reconciling" explanations for the mechanisms of action of "low doses" have been proposed. Most often, researchers - biologists assumed that that a certain number of molecules of the original substance could be preserved during the preparation of “high dilutions” due to near-wall mechanisms or uneven distribution of molecules in the surface and deep layers of the solvent, or the molecules could be preserved in dissolved air microbubbles [7, 8]. Hypotheses have been put forward that even a small amount of molecules preserved in dilutions is capable of exerting a significant effect through the mechanisms of intracellular signal amplification; L.A. Blumenfeld proposed [9] that the increase in the activity of "high dilutions" occurs through the mechanisms of parametric resonance, which is close to the concept of hormesis popular in homeopathic literature. or the molecules could be preserved in dissolved air microbubbles [7, 8]. Hypotheses have been put forward that even a small amount of molecules preserved in dilutions is capable of exerting a significant effect through the mechanisms of intracellular signal amplification; L.A. Blumenfeld proposed [9] that the increase in the activity of "high dilutions" occurs through the mechanisms of parametric resonance, which is close to the concept of hormesis popular in homeopathic literature. or the molecules could be preserved in dissolved air microbubbles [7, 8]. Hypotheses have been put forward that even a small amount of molecules preserved in dilutions is capable of exerting a significant effect through the mechanisms of intracellular signal amplification; L.A. Blumenfeld proposed [9] that the increase in the activity of "high dilutions" occurs through the mechanisms of parametric resonance, which is close to the concept of hormesis popular in homeopathic literature.

Another most common explanation was the assumptions about the ability of the solvent to retain the properties of the substance eliminated from it - the “water memory” hypothesis, which is based on the idea of water structuredness (using such terms as clusters, clathrates, disequilibrium, chirality, coherent domains, dissipative structures , supramolecular ensembles, nanoassociates, etc.) or, in other words, the presence in the solvent of a material matrix that carries information about the properties of a substance that is already absent in the dilution [10–18]. The presence of signs of structuring of water or other solvents has been shown in a fairly large number of studies of the physical or physicochemical properties of “high dilutions” using various analytical methods (mainly spectral) [19–24]. Clusters of different sizes were found depending on the methods used. Most authors see the rearrangement of solvent hydrogen bonds as the basis for the formation of clusters [25]. Some researchers suggest that clusters preexist in the solvent; others that they are formed during the stepwise dissolution of the original substance. At the same time, it was found that not all solvents can be used for the preparation of biologically active preparations [26]; nanoassociates are not formed in all of them [10]. It is assumed that "high dilutions" are capable of remote (according to resonance mechanisms) interaction with biological objects, and various variants of such interaction are possible. Some authors believe that structured dilutions that carry information about the eliminated substance have an impact directly on the target of this substance in the body; others, that the impact is directed at the complex, hierarchically organized internal water environment of the organism [27–29].

Of the brightest representatives of the phenomenological stage of the study of "high dilutions", first of all, I would like to note well-known domestic scientists who managed to step over the nihilism existing in the scientific community towards homeopathy and "high dilutions" in general - academicians of the pharmacologist N.P. Kravkov, physiologist I.P. Ashmarin, chemist A.I. Konovalov.

N.P. Kravkov almost a hundred years ago, using a model of an isolated organ (ear), showed that “high dilutions” of various drugs affect blood flow [30]. Our contemporary, the famous physiologist I.P. Ashmarin conducted a large series of experimental work with various biologically active substances in "high dilutions" and showed that they are capable of inducing certain molecular and cellular effects; suggested a hypothesis about cascade intracellular mechanisms of amplification (amplification) of the action of “small doses” [31, 32]. Academician A.I. Konovalov et al., predominantly using the method of dynamic light scattering, showed the presence of nanosized molecular ensembles in “high dilutions”; established that for their appearance it is necessary to dissolve the initial substance in the presence of an electromagnetic field [10].

Great interest in the scientific community was caused in 1988 by the publication in the journal Nature article by Jacques Benveniste and co-authors, in which they reported that they managed to cause a well-known immunological phenomenon - degranulation of basophils,

acting on them with a “high dilution” of antibodies to immunoglobulins E [33]. Subsequently, in the presence of a specially created commission, the result was not reproduced, which caused a violent reaction in the scientific world, and increased the wary attitude towards “high dilutions” and homeopathy [34]. Homeopaths, in turn, put forward the theory of a malicious conspiracy against them. In laboratory conditions, there may be cases where the experiment cannot be repeated both with traditional doses and with "high dilutions". For example, there may be a change (decrease) in sensitivity to a particular dilution of an investigational product. In the future, when the dilution is replaced by another, the effect may reappear, which correlates with the observations of E.B. Burlakova [35]. Therefore, we prefer to use a mixture of several dilutions to increase the stability of the results. The reproducibility of results also depends on the type of carriers used for highly diluted preparations: solid forms are more stable than liquid ones; water-alcohol mixtures are more stable than aqueous dilutions. Another feature of "small doses" is that the body's sensitivity to them is much higher than that of individual biological objects, tissues or cell cultures used in the experiment. But the main reason is probably the special direction of action of "high dilutions". Their direct - modifying (against the background of the original substance) action is reproduced much better than the "secondary" molecular cellular effects caused by them. Another feature of "small doses" is that the body's sensitivity to them is much higher than that of individual biological objects, tissues or cell cultures used in the experiment. But the main reason is probably the special direction of action of "high dilutions". Their direct - modifying (against the background of the original substance) action is reproduced much better than the "secondary" molecular cellular effects caused by them. Another feature of "small doses" is that the body's sensitivity to them is much higher than that of individual biological objects, tissues or cell cultures used in the experiment. But the main reason is probably the special direction of action of "high dilutions". Their direct - modifying (against the background of the original substance) action is reproduced much better than the "secondary" molecular cellular effects caused by them.

A special place in the history of the study of "high dilutions" is occupied by the works of E.B. Burlakova, who showed the effect of various drugs in “high dilutions” on the electrical activity of neurons, peroxidation, and other physiological processes and suggested that one of the mechanisms of sensitivity to “low doses” may be the functional rearrangement of the active centers of enzymes [35, 36]. Being a specialist in the field of low-intensity fields, Elena Borisovna not only revealed the various biological effects of highly diluted preparations, but also for the first time identified properties common to “high dilutions” and weak field effects:

- non-monotonic, polymodal dependence "dose effect". In most cases, activity maxima are observed in certain dose intervals separated by the so-called "dead zone";
- a change in the sensitivity (as a rule, an increase) of a biological object to the action of various SMDs (“super-low doses”);
– a manifestation of kinetic paradoxes, namely the ability to catch the effect of SMD of biologically active substances when the same substance is present in the cell or in the body at doses several orders of magnitude higher, as well as the effect on the receptor of a substance at doses orders of magnitude lower than the dissociation constants of the ligandreceptor complex ;
– dependence of the "sign" of the effect on the initial characteristics of the object;
- "stratification" of the properties of a biologically active substance as its concentration decreases, at which activity is still preserved, but side effects disappear.

The last property is the “stratification” of the effects of “high dilutions” into

at the clinical level - homeopaths can also observe during proving (individual reactions reproduce in a reduced form the picture of intoxication with the same drug used in toxic doses).

III. TARGET STAGE

As noted above, we found that all "high dilutions" differ from the original substance not so much quantitatively as qualitatively: they have a common property - a modifying activity that is absent in the original substance [37].

The modifying activity was revealed in the study of various pharmacological drugs - prednisolone, diclofenac, haloperidol, cyclophosphamide, etc. Each of the drugs was administered to animals in the experiment simultaneously with the "high dilution" of the same drug, and in most cases the "high dilution" enhanced the pharmacological effect of the drug and reduced its toxicity [38–49].

These results indicate that the technology of the so-called "potentiation" proposed by S. Hahnemann leads to the appearance in the solvent of new properties that are absent in the original substance. Therefore, homeopathic technology cannot be identified with the dilution process in its classical sense, since, we repeat, the products of this technology differ from the original substance not quantitatively, but qualitatively. As a result, it is incorrect to call them “small doses”, since a dose is a part of a substance that has the same properties, and “high dilutions” after technological processing are a material object different from the original substance.

In the literature, a conditional division of dilutions into high, containing, according to the Avogadro number, any amount of the starting substance, and ultra-high, “going beyond” the Avogadro number, is accepted. E.B. Burlakov, based on the theoretical ability of biologically active substances to have an effect at a concentration of 10^{eleven}, $10^{12}$and even at $10^{thirteen}$M, considers these concentrations to be "small" doses, and concentrations of $10^{thirteen}$M and below are paradoxical, since at such concentrations the van't Hoff mass action law ceases to work, and the concept of "concentration" loses its meaning [35].

In fact, such a division into “small and ultra-low doses”, “high and ultra-high dilutions” is rather speculative, since the modifying effect does not depend on whether the original substance is preserved in the dilutions or not. The stability and reproducibility of the effects of "high dilutions" depends on the characteristics of the technology of their preparation, and not on the amount of the original substance preserved in them. In the process of preparing “high dilutions”, there is not an increase (potentiation) of the properties of the original substance, but the appearance of new properties, therefore the term “potentiation” itself, which came from homeopathy, is also not entirely correct from modern positions. To emphasize the release of a new type of activity during the technological processing of the starting substance, we propose to use the terms "release activity" (RA),

drugs." It is most appropriate to use the term “release activity” for targeted drugs (drugs whose action is directed at certain target molecules in the body) studied in accordance with modern requirements for pharmacological drugs and, as a result, having pathogenetically substantiated (nosological) indications for use [50].

For release-active remedies used on the basis of proving data, the name "homeopathic remedy" should of course be retained, emphasizing that the remedy is intended for individual use in sensitive patients. Such drugs cannot have "nosological" indications for use.

In complex homeopathic preparations, another common property of “high dilutions” is used - tropism for certain organs, tissues or physiological processes in the body. Data on tropism are obtained empirically - in the course of the therapeutic use of such drugs, they practically cannot be proven experimentally. If complex homeopathic remedies have their stated indications, their effectiveness can potentially be clinically proven.

The leading role of the technology process is emphasized by the following fact: ordinary purified water subjected to technological treatment in the form of multiple sequential dilution acquires new properties that are different from intact pH water: electrical conductivity, surface tension, spectral characteristics, sound propagation speed.

Unlike technologically treated water, a (potentiated) drug has a highly specific effect: such drugs act only on the original substance (both in the body and in vitro). So, on the example of "high dilutions" of antibodies to interferon gamma using NMR spectroscopy, it was shown that the effect of RA antibodies to interferon-gamma on its target - interferon-gamma molecules is based on a change in the spatial (conformational) characteristics of the target molecule, the probable cause of which is the interaction according to the resonance principle. This effect is a trigger and leads to the activation of the usual interferon-gamma signaling pathway. Simply put, instead of introducing interferon-gamma into the body, we used a catalyst that enhances the binding of endogenous interferon-gamma to its main target [50].

DISCUSSION AND CONCLUSIONS

The specificity of exposure in pharmacology is a natural property of any substance (drug). But at the same time, RA (potentiated) drugs also have features characteristic of field effects. This is, first of all, the speed of response: when RA morphine or RA ethanol were introduced into the oral cavity of experimental animals, we recorded instantaneous changes in the EEG of animals or the frequency of hypothalamus self-stimulation in animals with electrodes implanted in the brain [51, 52]. To provide an instant psychotropic effect, it turned out to be enough to hit the minimum volume - a drop of RA dilutions on the oral mucosa, which indicates its ability

penetrate tissue barriers and also indicates the remote (field) nature of the impact.

Studies of RA dilutions of preparations show that in the process of their preparation (potentiation) there is not a decrease in the amount of the initial substance, but the transition of the substance into a new quality, a new physicochemical state, which is associated with the solvent, can be transferred to a solid carrier and is able to maintain activity for a long time [50].

Thus, to date, the reality of the physiological (biological) effects of "high dilutions" has been repeatedly shown, and the modifying nature of their action has been revealed; it was demonstrated that this activity is technogenic; the possibility of using "high dilutions" to create targeted biological preparations has been proven. The peculiarity of the current state of the problem of "small doses" is that the research methods available in biology and medicine have exhausted themselves. The phenomenology of the effects of release active dilutions has already been established. The next word belongs to theoretical physics. Only after understanding the physical nature of release activity can the phenomenon of homeopathy itself be explained, the biological basis of which, in our opinion, is a special dual individual-specific spatial (physical) organization of the organism [53].

CONFLICT OF INTEREST

Epstein O.I. is the scientific director of the research and production company MATERIA MEDICA HOLDING, which develops and sells drugs based on release active antibodies.

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Author's address

Epstein O.I. - Scientific Director of NPO "Materia Medica Holding", Professor, Doctor of Medical Sciences, Corresponding Member of the Russian Academy of Sciences, Laureate of the Prize of the Government of the Russian Federation"

science@materiamedica.ru

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