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The State of Basic Research on Homeopathy

Stephan Baumgartner

Introduction

This review gives an overview of the main topics and problems of basic research on homeopathy. The present review is by its nature qualitative and narrative. It is based upon several years of professional experience, and I will try to focus on the standard of knowledge and the major problems in this field of research and to identify the main obstacles to scientific progress. This review does not claim to be comprehensive; experimental work is always cited as a representative example. More formal reviews aiming at completeness and trying to assess quality and reliability of the research carried out by application of scoring systems have been published elsewhere for different areas of basic research[1–4].

Historically, basic research on homeopathy has been defined as using laboratory methods and models to assess basic homeopathic principles. This means that any research involving humans as entire beings is not covered by basic research. I will adapt this definition of basic research throughout this article.

The main homeopathic principles, developed by Hahnemann more than 200 years ago, are described in detail in the first chapter of this book. In a condensed form, they can be defined as the famous three pillars of homeopathy: (1) the law of similars, (2) homeopathic remedy provings (homeopathic pathogenetic trials), and (3) the principle of potentization. In short: in human homeopathic therapy, diseases are treated by application of substances in the lowest possible dose [potentization], with the selection of the appropriate substance being based on the best possible correspondence [law of similars] between the entirety of the symptoms experienced by the patient and the symptoms produced in healthy humans after exposition to a certain substance, in substantial or potentized form [remedy proving].

The integration of these three basic principles of homeopathy into the current scientific paradigm is very difficult. The most prominent challenge is the principle of potentization since it implies that the medical power of a drug can be increased by serial dilution and succussion. The challenge is especially pronounced for homeopathic preparations beyond 24x or 12c ("Avogadro's number") where the probability to find even a single molecule of the potentized substance rapidly approaches zero.

The law of similars is also questioned by present day science. However, it is less in focus of critical inquiry since the principle of potentization represents a stronger provocation. The possibility of remedy provings (the first pillar of homeopathy) is only questioned when high homeopathic potencies (e. g. 30c) are used. Conventional human toxicology can be seen as a collection of drug provings.

Basic research on homeopathy is most often carried out to either prove, disprove or investigate the validity of the homeopathic principles being in conflict with modern science. Correspondingly, most basic research investigations deal with the principle of potentization, and only a few with the law of similars. Analogously, only very few remedy provings were undertaken using material doses in laboratory organisms for primarily homeopathic research interests.

In addition to the investigation of the mere experimental evidence for the potentization and the law of similars, fundamental aims of basic research can be seen as (1) to enlighten the mode of action of homeopathic preparations and (2) to develop tools to ensure product quality (e. g. regarding shelf live, external potentially disturbing physical influences, etc.). This corresponds to a twofold approach, a basic scientific and a pragmatic pharmaceutical approach.

There are several publications of high methodological quality that document experimental evidence for the principle of potentization. However, attempts to independently reproduce published findings by other research teams have often either failed or resulted in inverted or altered effects. Even laboratory-internal reproducibility seems to be a non-trivial task. Thus the most prominent problem encountered by

scientists working on homeopathic principles is reproducibility. This will be illustrated by several examples and discussed in the next chapter.

Implicitly related to the problem of reproducibility is the challenge of test system stability. From a conventional point of view higher homeopathic potencies are nothing but dilution medium (e. g. water or water/ethanol-mixtures), and any experiment will show nothing but the background noise of the experimental system and all kind of systematic errors due to inhomogeneities in space and time. Therefore it is of ultimate importance to demonstrate that any given experimental set-up is stable and does not produce any artifacts, i. e. false-positive results. This can be accomplished by regularly performing so-called systematic negative control experiments as elaborated and discussed in the third chapter.

The third major problem is the choice of adequate controls, which depends on the scientific question to be studied. The succussion step of potentization involves a bunch of physicochemical processes such as dissolution of materials from the potentization vessel walls and from ambient air. All these processes are unspecific in the sense that they are common to all homeopathic preparations and are not specific to the substance potentized. Thus, the use of unsuccussed solvent as only reference is in general not suitable to document specific properties of homeopathic preparations. A more detailed elaboration of the topic of adequate controls is given in the fourth chapter.

Science is generated by human cognition which involves not only observation of phenomena but also thinking and ideas. Primarily the latter enter textbooks in the form of classifications of phenomena, hypotheses, mathematical descriptions, formal theories, and philosophical considerations. Hypotheses and theories are furthermore advancing development of science by guiding observation and designing experiments. In homeopathic research, there seems to be a lack of interplay between theory and experiment (fifth chapter).

Which laboratory model systems are best suited for investigation of homeopathic preparations? This question is also unanswered so far.

The current scientific paradigm sees cells and genes as the primary cause for everything that happens within an organism. From the results published so far, however, one can gain the impression that more complex systems (e. g. animals and plants) show stronger reactions to homeopathic interventions than simpler systems (microorganisms, cell lines, etc.). Another question concerns the state of the system, since it seems that healthy organisms react less pronounced to homeopathic preparations than diseased or stressed organisms. Advantages and drawbacks of different approaches, including the question of optimal outcome measures, are discussed in the sixth chapter.

Finally, there is a lack of resources. Primarily, there is a lack of scientific working groups continually engaged in homeopathic basic research; the "critical mass" necessary for fruitful development has not been reached yet. This is due to several reasons. There is no tradition in universities to carry out basic research on homeopathy, mostly due to the incompatibility of homeopathic principles with current scientific knowledge. Furthermore, preconceptions and social control embarrass implementation of homeopathic research projects. In addition, government and other official funding is difficult to obtain. Promotion is therefore mostly restricted to foundations and smaller homeopathic companies not belonging to the pharmaceutical global players with corresponding resources.

Evidence for the principle of potentization: the quest for reproducibility

The principle of potentization essentially states that the medical power of a drug can be increased by serial dilution and succussion. One might thus expect a continuous positive correlation of medical power and potency level. Most clinical investigations focused on a much simpler question, however: Is there a medical power of highly diluted drugs at all? As shown in the other chapters of this book, there are indeed a certain number of single (or small series of) clinical trials for certain medical conditions that give an affirmative answer to this question. This fact is a considerable challenge for modern science.

Compared to clinical research basic research has the clear advantage that one can study the topic in question by using fewer resources. There is certain number of high-quality scientific publications from basic research experiments showing that potentized drugs can exert specific effects. This is an indication that the drugs investigated are different from other potentized substances or potentized dilution medium. In addition, the putative correlation of effect size and potency level has been investigated in several experiments. Table 1 lists some corresponding high-quality experiments that were either selected from formal reviews[1–4] or published more recently. Interestingly, in almost every investigation that was able to identify specific effects of homeopathic preparations a discontinuous and nonlinear relation between effect and potency level was observed, i. e. there were active and inactive potency levels alternating in seemingly irregular sequence.

Based on these investigations one is tempted to conclude that there is indeed experimental evidence for specific effects of homeopathic preparations also in laboratory model systems. In order to increase the level of evidence, however, independent reproductions are often called for. But this seems to be difficult to achieve. In fact, I do not know any experimental model that has successfully been replicated in an independent trial. As exemplified below, many replication trials failed or resulted in inverted or altered effects.

Betti et al. observed growth and germination rate enhancement of wheat poisoned with arsenic and treated with arsenic 45x in several independent experiments[11, 20–22], whilst Binder et al. observed growth and germination rate diminution in a very similar experimental setting in a carefully designed replication trial[10]. The reasons for this effect inversion are still unknown.

First author	Year	System	Material treatment	Potentised substance	Potentised control	Significant effects	Relation effect to potency level
Baumgartner[5]	2004	Dwarf peas	None	Gibberellic Acid	Water	Increase growth	Discontinuous
Witt[6]	2005	REDEM	n.a.	Silicea, Argentum nitricum	Diluent	Alteration amplitude	n.a.
Belon[7]	2004	Human basophils	None	Histamine	Water	Inhibition degranulation	Discontinuous
Benveniste[8]	1991	Human basophils	None	Anti-IgE	Anti-IgG	Increase degranulation	Discontinuous
Betti[9]	2003	Tobacco	Mosaic Virus	Arsenicum album	Water	Alteration lesion number	n.a.
Binder[10]	2005	Wheat	Arsenicum album	Arsenicum album	Water	Decrease growth	n.a.
Brizzi[11]	2000	Wheat	Arsenicum album	Arsenicum album	Water	Alteration germination rate	Discontinuous
Delbancut[12]	1994	Pig kidney cells	Cadmium, Cis-Platin	Cadmium, Cis-Platin	Medium	Cell protective effect	Discontinuous
Demangeat[13]	1992	NMR relaxation	n.a.	Silicea	Diluent	Increase T_1	increasing
Demangeat[14]	2004	NMR relaxometry	n.a.	Silicea	Diluent	Alteration T_1	Discontinuous
Endler[15]	2003	Frog	Thyroxine	Thyroxine	Water	Decrease metamorphosis	n.a.
Jonas[16]	2001	Rat neurons	Glutamate	Glutamate	Medium	Cell protective effect	Discontinuous
Scherr[17]	2006	Yeast	None	Azoxystrobin, Phosphorus	Water	Decrease growth	Discontinuous
Wälchli[18]	2006	Lymphocytes	Cadmium chloride	Cadmium chloride	Water	Increase cell viability	n.a.
Zausner[19]	2002	Frog	None	Thyroxine	Water	Decrease metamorphosis	n.a.

Table 1: Examples of high-quality experiments with results in favor of specific effects of homeopathic potencies. All experiments listed used succussed or potentized controls. The list is not comprehensive; n. a. = not applicable

Degranulation of human basophilic blood cells was used as a model in a large number of experiments. Davenas et al. observed strong and seemingly reproducible induction of basophil degranulation through homeopathic potencies of anti-IgE[23]. In a strictly blinded follow-up study Benveniste et al. compared potencies of anti-IgE with potencies of anti-IgG and observed significant effects in six out of 18 single experiments, but the effects of the different potency levels varied from experiment to experiment, i. e. they were not reproducible. Nevertheless, a significant mean basophil degranulation induction could be observed across all experiments[8]. Hirst et al. compared succussed dilutions of anti-IgE with unsuccussed anti-IgE dilutions as well as potentized buffer and observed varying effects of anti-IgE as a function of potency level in some but not in all experiments. Averaging all experiments no significant differences between the potency levels investigated were observed[24]. Ovelgönne et al. compared succussed and unsuccussed dilutions of anti-IgE and observed no significant mean difference between these two types of dilutions[25].

Another model using human basophilic blood cells investigates the effects of highly diluted histamine on the degranulation of activated basophils. A blinded multi-center study using alcian blue staining resulted in an overall highly significant inhibition of basophil degranulation[7]; however, active and inactive potency levels differed for each study center[26]. The same basic study design was methodologically refined by the introduction of flow cytometric methods replacing visual basophil counting. Several studies[27–30] again observed inhibition of basophil degranulation by high dilutions of histamine. But there was one exception[31]. Again, active and inactive potency levels differed for each study[31].

There may be several causes for the lacking reproducibility as outlined above: artifacts, uncontrolled relevant parameters, inappropriate outcome measures, or system-inherent irreproducibility.

Artifacts (meaning false-positive results) can be due to contamination, systematic drifts or stochastic noise of the experimental set-up, which are wrongly interpreted as treatment effects. Correspondingly,

results of earlier studies cannot be reproduced by follow-up studies with better methodology. In order to be able to exclude artifacts due to a singular contamination during the production process it is recommended to always test several independent production lines of homeopathic potencies. To securely exclude artifacts from systematic or stochastic errors one has to be sure about the stability of the experimental system used. This point is discussed in more depth in the next section.

For a given experimental system there are often many factors that influence the response of the system. For example, electrostatic phenomena may be influenced by humidity and other quite unexpected factors such as the shoe soles of the experimenter. Therefore, irreproducible effects will frequently occur when not all natural laws governing a certain scientific field are known. Since the mode of action of homeopathic preparations is yet unknown there is no definite knowledge about optimal production and storage procedures. Thus, there is always the possibility of inefficient remedies with consequent negative results in experimental investigations.

In addition, one study reported that the homeopathic "information" seemed to be able to spread through sealed glass ampoules[32]. If this phenomenon can be confirmed also in other systems, so far undiscovered cross-contamination may lead to false-negative results and correspondingly to lacking reproducibility. Unknown parameters may also be crucial for the response of the experimental system used for investigation. So far, I know two model systems where at least one relevant parameter could be identified: the amphibian model and the dwarf pea model. In the amphibian metamorphosis model developed by Endler[33] only animals from high-land biotopes consistently respond to a treatment with homeopathically potentized thyroxin[34], presumably due to a higher endogenous level of thyroxin. In the dwarf pea model seed quality (supposedly premature harvest) was identified as relevant trigger factor for a response to a treatment with homeopathic preparations of gibberellic acid[35]. For the basophilic blood cell model discussed above donor specificity might be a parameter worthwhile investigating.

Betti et al. recently proposed variability of a system's response as a more consistent outcome parameter than the mean response[36]. The idea behind this concept is that homeopathic preparations primarily act in a system-regulating way and generally decrease scatter, whilst mean values may be left unchanged. Their collection of examples corresponds well to that hypothesis; there are, however, other investigations which do not fit[10, 35]. Possibly the latter examples can be integrated in a modified or more sophisticated form of the theory.

Irreproducibility can also be system-inherent. Well-known examples from physics are chaotic systems and quantum mechanical systems. Whilst the former systems are still deterministic by nature the latter are inherently indeterministic. It is important to note that these examples demonstrate that innate irreproducibility is no obstacle for scientific exploration. Adapting the signifier theory of Bastide and Lagache[37] a system will give coherent responses to stimuli only when the information transferred has an interpretable and important meaning for the system. Less important information may disturb the system in an unspecific way and correspondingly yield inconsistent effects only.

Which of the four possible reasons was or were responsible for problems with reproducibility in a certain experimental investigation can be determined by repeated careful experimentation in several independent research groups and by deepened theoretical considerations.

We are faced with a complex situation that needs to be disentangled since the solution of the problem of reproducibility involves all other points discussed beneath: test system stability, adequate controls, lack of theories, experimental design, and lack of resources. Since all these issues are linked, an iterative approach is called for.

The challenge of test system stability

In homeopathic basic research experiments effects are often quite small. Since the size of the effects may be in the same order of magnitude as

the natural variability (the "background noise") of the experimental system, the probability of systematic and stochastic errors increases considerably. Stochastic errors can be caused by the natural growth variability of cells and plants, or the measurement error of an instrument. Systematic errors may arise from spatial inhomogeneities within the experimental set-up (e. g. in temperature, humidity or illumination) or from temporal drifts (e. g. of measuring instruments), but also from human factors like observer bias. The latter can be excluded if the treatments are coded and unknown to the experimenter. Therefore, blinding should be standard in any investigation of homeopathic potencies.

Systematic and stochastic errors are usually minimized by using randomization and an adequate statistical evaluation. This procedure is fine for proper evaluation of mean effects across a series of single experiments. Possible systematic errors will then manifest as increased scatter of measurement values and cancel out in mean calculations. In a more detailed statistical analysis like analysis of variance, however, systematic errors may show up as significant statistical interactions between treatment effects and the experiment number. This is no problem as long as one looks only for reproducible treatment effects on mean values.

However, as discussed in the preceding section, there seem to be many cases in homeopathic basic research where effects are either modulated by still unknown parameters or inherently stochastic by their very nature, thus leading to seemingly irreproducible results. When adapting the procedure of elimination of systematic errors by randomization only the systematic errors get mixed up with the unknown homeopathic effect modulating factors because both influence experimental outcome. It is thus not possible to determine whether variability in mean values is due to randomized systematic errors or due to "true" variability of effects.

One solution to this problem is the thorough implementation of systematic negative control experiments (SNC)[38]. SNC is a typical full-size experiment where the usually different treatments are replaced by

identical treatments. The experiment is then analyzed as usual, i. e. as if there were different treatments (parameters). Since all these parameters are from an identical source, statistical analysis should yield no significant differences. This is, however, only the case if there are no systematic errors. An example: A typical single experiment with the water plant duckweed[39] involves 100 beakers filled with plants, cultivation medium and homeopathic dilutions. Usually, 20 different treatments (e. g. three controls and 17 potency levels of a given substance) are tested in five replicate beakers each. In SNC all 100 beakers are involved, but all 20 treatments are identical, e. g. distilled water from the same batch. The experiments are then analyzed for differences between these 20 identical treatments. In case there are none the results yield the proof that the experimental system is stable. In case there are significant differences one has to conclude that there is a not adequately controlled external influence disturbing the system, like e. g. a difference in temperature or illumination in the growth chamber used, which leads to false-positive results (artifacts). In such a case the experimental set-up has to be revised in order to eliminate these inhomogeneities.

In case that one can provide data from a series of systematic negative control experiments, which furnish evidence for the stability of the experimental set-up, one can conclude that seemingly irregular effects observed in experiments with homeopathic samples are real treatment effects modulated by unknown factors; they are not artifacts due to randomized systematic errors[17]. In that case one has good reasons to perform further investigations to identify these influencing factors. Thus, test system stability is an indispensable precondition for homeopathic basic research.

The choice of adequate controls

In basic research, effects of homeopathic preparations have been compared with different controls: unsuccussed solvent, succussed solvent,

potentized solvent, and other substances (in potentized form or material concentrations). Different potency levels of the same substance have also been used. The choice of the appropriate control depends on the research question under study.

Investigations of the law of similars involve characterizations of the effects of different substances in material or potentized form on healthy organisms. Correspondingly, there is the need to include a lot of substances as mutual controls to obtain a broad database of different symptoms. In a second step, diseased organisms have to be treated by different substances (in material or potentized form). Again, a lot of substances need to be tested as mutual controls in order to document the validity of the Law of Similars.

The homeopathic principle of potentization includes the controversial presumption of specificity, i. e. the notion that homeopathic potencies carry some sort of memory of the substance potentized. This hypothesis can be tested by comparison of the homeopathic potencies under question with homeopathic potencies of other substances produced under similar conditions. As an example, the effects of Arnica 30c could be compared with Sulfur 30c.

Another research topic is the relation between effect and potency level. For example, one can study the questions whether Arnica 6c, 15c and 30c have different effects, or whether there is a continuous relation between adjacent potency levels (e. g. all potency levels of Silicea between 6c and 30c). In this case, comparisons have to be drawn between the different potency levels. Specificity can be additionally addressed by simultaneous testing of homeopathic potencies of other substances, preferably at the same potency levels.

The use of unsuccussed solvent as only reference is in general not suitable to document the specificity of the principle of potentization. This is due to the fact that the succussion step of potentization involves a lot of physicochemical processes, such as increased dissolution of materials (inorganic ions, plasticizers, etc.) from the potentization vessel walls, dissolution and suspension of ambient air (with consequent changes in pH due to CO_2 dissolution, microbial contamination, etc.),

and even cavitation (leading to radical formation and oxidative processes). All these processes are unspecific in the sense that they are common to all homeopathic preparations and not specific to the substance potentized. If it could be shown that the effects of succussion on the solvent do not influence the chosen experimental system, unsuccussed solvent could also be used as control.

Based on the available literature, it seems that microorganisms and plants are not sensitive to water succussion effects[5, 17, 35, 39]. This has to be studied for every system, however. For pot and field trials unsuccussed solvent seems to be a possible valid control because of the large buffering capacity of the cultivation substrate usually used. For physicochemical research, however, the use of succussed controls is indispensable due to the much higher sensitivity towards the succussion effects discussed above.

Another possible control for the investigation of the principle of potentization is potentized solvent, applied in the same potency levels as the homeopathic preparation (e. g. 30c). This means that a homeopathic dilution is prepared according to standard procedures – except for the first dilution step where the homeopathic drug is replaced by the solvent itself. At first glance this preparation seems to be perfect as control for any homeopathic preparation. But this is only true if the potentized solvent itself has no homeopathic effect. Since lactose, ethanol and certain mineral springs are listed in homeopathic repertories the seemingly perfect control becomes less suitable. Indeed, effects of potentized solvent were observed in several investigations[9–11]. The late Madeleine Bastide attributed this to the special properties of water which is open to any kind of information to be picked up during the potentization process if there is no dominant signal from a mother tincture. This hypothesis should be investigated more closely.

Some years ago, the combined use of unsuccussed and succussed solvent was proposed[38] for investigating the principle of potentization. It was also implemented in several investigations[5, 17, 35, 39]. This suggestion was based on the idea that the above-mentioned unspecific physicochemical effects are associated with the agitation step only, but not

with the dilution step. Therefore, the idea of a control consisting of agitated but not diluted solvent was raised in order to circumvent the problems associated with potentized solvent as discussed above. Since 90 % or 99 % (depending on decimal or centesimal potentization) of the material of a given homoeopathic potency consists of solvent that has undergone agitation only once, it may be sufficient to succuss the control only once, i. e. in the same way as the last potentization step was performed. With regard to leached inorganic ion content[40] a one-time succussed control proved equal to a repeatedly succussed control. It can, therefore, be assumed that this would also be true for other physicochemical succussion effects. In case of indistinguishability of unsuccussed and succussed solvent both controls may be pooled for final statistical evaluation; in case of differing effects the procedure to be followed is outlined elsewhere[38].

Finally, for the investigation of the principle of potentization the importance of using samples (potencies and controls) made of the same batch of solvent cannot be stressed enough, because different batches of solvent (water, ethanol, etc.) may vary in chemical composition.

Lack of interplay between experiment and theory

Science advances by the interaction of observation and theory. Empirical observations are the indispensable basis of any science, theory helps to classify and understand the phenomena observed. Thus, both are guided somehow by each other. In particular, theory may help to direct observation and to design experiments (see also next section).

In homeopathic basic research, it seems to me, these two fields are still far apart. There are a lot of theoretical approaches to integrate the homeopathic basic principles in a more elaborated theoretical framework[37, 41–46]. But I know only very little experimental work which explicitly relies on a theory, or tries to test a hypothesis or a prediction developed from a theory[47]. Analogously, I know only very few theories developing predictions amenable to empirical testing.

Hitherto the best example of an integration of observations into a more general theoretical framework seems to be the work of Bastide and Lagache[37]. However, their theory is still very general and descriptive, thus not easily allowing to directly deduce testable hypotheses.

On the other hand, the observational basis is still not broad enough to foster the development of a good theory. There seems to be a hen and egg problem: without observations it is difficult to develop a good theory, and without theory it is difficult to design good experiments. This dilemma can only be overcome by a boost in both experimental and theoretical work, and by intensified collaboration.

General design of experimental systems

Apart from the problems of adequate controls and system stability the more general question about choosing the laboratory model systems best suited for the investigation of homeopathic preparations is still unanswered.

The current reductionist scientific paradigm considers cells and genes as the primary cause for everything going on in an organism. Correspondingly, modern research focuses on effects on genomic and cell level and frequently uses cell lines as study material.

The results published so far indicate that more complex systems (e. g. animals and plants) show stronger reactions to homeopathic interventions than simpler systems (microorganisms, cell lines, etc.). Jonas et al., for example, observed that some homeopathic remedies seemed to significantly reduce cancer incidence and mortality in rats injected with prostate cancer cells, whereas the same homeopathic drugs had no direct cellular anticancer effects whatsoever in vitro[48]. In addition, cancer cell lines seem to respond less to homeopathic preparations than healthy cells[4, 18].

These observations may be related to the concept of Bastide and Lagache[37] stating that homeopathic remedies act on the level of the body-internal regulation network responsible for life and self-healing. The more complex a system is the more sophisticated and differentiated are the auto-regulation pathways for system control, and the larger is the potential for possible answers of the system to homeopathic treatments. According to Bastide's and Lagache's theory cancer cells emancipated from the body-internal system control, and correspondingly would also be non-responsive to homeopathic treatment.

It would be very useful to compare the response of systems of different complexity and organizational level to homeopathic treatments in more studies. The results will not only yield evidence for the importance of the "systems complexity factor" for the design of homeopathic model systems, but will also advance the knowledge about the nature of homeopathic effects.

From the literature one can also gain the impression that organisms react more strongly to homeopathic treatments when the system is somewhat out of balance. I know of only few studies, however, which directly compare healthy with stressed or diseased organisms regarding their response to homeopathic treatment[11, 15]. Some additional studies directly addressing this question would be very helpful for the selection of efficient model systems as well as for elucidation of the nature of homeopathic effects. In case of confirmation of the above-mentioned presumption the action of homeopathic potencies would be regulative in nature.

There is, however, some support for the notion of a regulative effectiveness of homeopathic preparations. In several botanical experiments data analysis of the effects of homeopathic treatments extended not only on the mean but also on the entire data distribution. In some studies scatter (intra-experimental variation) was reduced under homeopathic treatment[36]; in other studies smaller plants seemed to profit more from a homeopathic treatment than larger plants[5]. There is even some indication towards a reduction of inter-experimental variation[9]. These results are pointing to a differential action of homeopathic preparations

depending on the state of the experimental subject. A corresponding data analysis of forthcoming experiments is strongly recommended, provided the number of treated subjects is large enough. Reduction of variability or homogenization of data distributions might even develop into a valid outcome measure which might prove to be more reliable than mean values[36].

A further important point in the development of good preclinical homeopathic model systems is the choice of the potentized substance. Due to the lack of a broad proving database for cells, microorganisms and plants, it is very difficult to use the law of similars to choose appropriate substances, i. e. with a correspondence to the state of system investigated. Approaches to solve this problem include the introduction of provings for cells[49], the use of phytotoxicological literature for the selection of remedies for a phytopathological system[50], the extrapolation of human drug provings to plants[5, 17, 39], the use of screening experiments to identify promising substances[5, 17, 39], and the introduction of chemical messenger substances (hormones) into experimental homeopathic research[5, 33, 51]. Especially the latter approach seems to have yielded fruitful results in several model systems, and seems worth further exploration.

The choice of appropriate methods to study physicochemical structure and dynamics of homeopathic preparations is also nontrivial. On the one hand, one could select standard methods established in water structure research[52] such as Raman and infrared spectroscopy, dielectric and thermodynamic properties, acoustic absorption and relaxation, neutron scattering, and nuclear magnetic resonance spectroscopy and relaxation. Some of these methods have been applied in homeopathic basic research, but so far only NMR relaxation studies[13, 14] yielded evidence for specific changes in the structure of the hydrogen-bond network of aqueous homeopathic dilutions.

On the other hand, there are also apparatuses available that were designed and constructed especially for the identification of homeopathic remedies. Unfortunately, the operation principle is not disclosed in most cases. Some of these devices have been investigated as black

boxes with partially interesting results[6, 53]. Due to the unknown operation principle the results of such apparatuses cannot be interpreted directly in scientific terms, and they are difficult to communicate.

It seems worthwhile to investigate any promising device more closely to identify its mode of operation. Due to the unknown mode of action of homeopathic preparations it is also possible that standard physicochemical methods for water structure are not ideal for the characterization of specific properties of homeopathic samples.

Conclusion

Homeopathic basic research uses laboratory methods and models to assess basic homeopathic principles, with a focus on the principle of potentization and the law of similars, though the latter is much less dealt with than the former. In the last years, quality und significance of the research carried out has steadily increased and thus allows some statements about applicability and validity of the principle of potentization in general science.

There is a considerable number of experimental investigations which provide evidence for specific effects of high homeopathic potencies. Interestingly, most of these studies observed a nonlinear and discontinuous relation between effect size and potency level, i. e. adjacent potency levels may differ considerably regarding their effects, with effective and ineffective dilution levels alternating in a seemingly irregular sequence. The question now arising is whether this is a pattern peculiar to basic research only, or whether this might have also significance for clinical applications.

The most prominent obstacle in homeopathic basic research is reproducibility. Most attempts to independently reproduce published findings either failed or resulted in inverted or altered effects. In principle, such a phenomenon could be explained by systematic or stochastic errors in precursor studies that cannot be reproduced by follow-up

studies with better methodology. I have the impression, however, that systematic or stochastic errors cannot be made responsible for all phenomena observed. There are many methodologically sound investigations reporting on effects of highly diluted substances. Thus, the major point to be addressed in forthcoming studies is reproducibility, laboratory-internal as well as -external. Research has to understand whether there are factors momentarily undetected, but in principle identifiable, determining the performance of the experimental system used, or whether irreproducibility is an inherent factor of homeopathic effects. The latter situation would be no basic obstacle for a scientific approach as can be learnt from quantum mechanics and chaotic phenomena.

The solution of the reproducibility problem requires, however, very solid experimental work with adequate controls using systems with documented stability. A large number of reproductions, internal as well as external, are necessary, presupposing patience and endurance from the researchers' as well as the sponsors' side. In addition, the experimental systems have to be steadily developed with a focus on possibly more reliable outcome measures. Finally, theorists and experimenters should work more closely together for a fruitful development of homeopathic basic research.

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