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Hormesis and its relationship with homeopathy

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Abstract

Homeopathy is an ancient and complex therapeutic method that is rediscovering its scientific foundations. Hormesis is a frequently observed phenomenon that has been rigorously reported with precise dose-response curves. The therapeutic method based on the principle of 'like cures like' should not be confused with hormesis, which has several different implications from those of homeopathy. Yet, because both these approaches to nature and medicine are very broad in scope, they do end up having some points of contact. Thus, the well-established and consolidated field of hormesis can help cast light, through its ideas and research methods, on the possible mechanisms of action of remedies in ultra-low doses.

Keywords

Hormesis, Homeopathy, High Dilutions, Similarity Principle, Ultra-low Doses

Introduction

Homeopathy and hormesis are two different concepts, because the former is a therapeutic method whereas the latter is a phenomenon inferred from careful observation of nature, and described through mathematical curves. Therefore, hormesis is not homeopathy, nor does it provide the 'explanation' for it. Homeopathy (as a therapeutic method) and hormesis (as a natural phenomenon) must each construct their own general theories and find their own specific mechanisms and explanations. Nevertheless, as well illustrated by Calabrese and Jonas,[1] there exist various points of contact that can suggest common avenues for future research. Often, the progress of science is inspired by analogies that reveal similarities between distinct systems: pre-existing knowledge of a – generally simpler – reference system (so called archetype) is used to construct working hypotheses for extending knowledge of a less well-understood – and generally more complex – system.

Hormesis

Science is an instrument for knowledge whose language is prevailingly quantitative and which has the specific episteme of creating 'symbols' for describing and interpreting reality. Consequently, the success of scientific theories is often also bound up with the symbols that they create and the words that they use, such as 'atom,' 'receptor,' 'antibody,' 'cytokines,' 'fractal,' 'apoptosis,' etc. These words evoke in our minds figures (symbols) that help us to think about the 'true' objects and phenomena of nature. Hormesis is a clear concept, with a simple definition, that is thus useful for describing a phenomenon that occurs in both natural reality and in laboratory (see note 1). The major symbols it employs are an upside-down U-shaped dose-response curve and a rebound curve over time; it makes extensive use of mathematical and statistical analysis. The word ('hormesis') and the symbols ('reverse U' and time-courses) are effectively and widely used for describing the relationship between living things (cells, tissues, entire organisms) and the chemical-physical world with which they come into contact. This approach applies to an extremely wide range of significant phenomena – from medicine to ecology – so that hormesis has justifiably gained increasing importance.

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Hormesis highlights certain phenomena (or facts, or experimental evidence) but does not itself constitute any sort of explanatory theory, least of all for homeopathy. Each example of hormetic curve requires its own explanatory theory, which identifies the 'mechanism' accounting for this behaviour of matter and living things, in the specific circumstances where it is observed. Precisely for this reason, the concept of 'hormesis' is a highly 'fertile' ground for stimulating research on phenomena ranging from gene expression to oncogenic risk and from microbiology to radiation pollution. Each of these fields can be explained through one or more mechanisms, which are today being explored with ever greater detail and thoroughness: transduction of extracellular signals into intracellular messages, molecular, cellular and tissue defence and repair systems, control of cell growth and cell death and neurobiology. These involve the formation of complex control networks – based on multiple and interacting feedback loops – that have the ability to adapt cell behaviour in extremely varied ways, making it possible to trace the self-regulatory mechanisms of the functions activated by different doses of the same substance.

This raises two issues with respect to hormesis, connected with its presumed significance and universality. For what concerns its significance, there is a tendency to regard hormesis as a 'compensatory' response to stress. Now, this may doubtless be true in many cases, but it does not constitute a rule. In some situations, hormesis may have explanations, causes and functions other than 'compensation': for example, at the cell level a hormetic phenomenon could be due to the fact that a cell may have two types of receptors (with high and low affinity) for the same substance; these two receptors could be coupled with transduction pathways that are respectively excitatory and inhibitory; likewise the differences in timing might not be due to 'compensatory' or 'rebound' mechanisms, but rather to the different speeds with which the two responses are activated: if the positive response to small doses involves protein synthesis or cell replication, it could easily be slower than, and hence occur subsequently to, the more rapid effect of inhibitory blockage. In this case, we cannot properly speak of compensation, but only of a simple overlap between two distinct pharmacological phenomena in the dose-response and time-course curves.

For what concerns the universality of the phenomenon, it must be said that though hormesis is very common, it is not observed unfailingly in every case. In our experimental work, especially in the laboratory, we have always borne in mind the possibility of 'discovering' hormetic phenomena in the behaviour of human leukocytes subjected to the most diverse treatments, and found it to often occur, under certain conditions, but not indiscriminately. For example, podophyllotoxin is a toxic substance that inhibits the function of granulocytes in high doses but stimulates it when used in low doses (such as those contained in homeopathic products); however, this stimulation does not occur when the cell function is activated with phorbol-myristate acetate; in this case, we observe only an inhibitory effect, without the hormetic effect.[2] Much more recently, we have described how quercetin, a natural substance found in foods, dose-dependently inhibits the function of basophils stimulated with anti-IgE antibodies (which simulate the allergic mechanism), without a hormetic effect; on the other hand, hormesis is observed, very clearly, when the cells are stimulated with bacterial peptides, and in that case the low doses of quercetin have an effect that enhances the response to the peptides.[3] This difference in the presence or absence of hormetic responses may have a distinct role in the pharmacologic regulation of inflammatory phenomena. Note that this consideration on the universality of scientific evidence also applies to homeopathy, and in particular to the principle of 'similars,' which is not true always and in every case but only under certain particular conditions.[4]

One limitation of the possible application of hormesis to homeopathic theories is the fact that hormesis – by definition – concerns substances which in high doses have a toxic effect. In reality, though, there exist substances with regulatory activity whose 'toxicity,' at least of direct type, is difficult to demonstrate. Consider for example neuromediators, hormones, cytokines and common mineral salts. Homeopathy does not use only diluted 'poisons' but also substances with modulating, regulatory action that are not direct toxins. What is more, in our experience (but also in the literature) there have been cases where a substance was found to have a stimulatory effect on a particular cell function when used in high doses, but an inhibitory effect when tested in low doses.[5-8] This 'reverse hormesis' is difficult to explain within a framework that assumes toxic effects of high doses, unless we consider the toxic effects to be the potential consequences on the entire organism of the substance in high doses. For example, in the cases we have cited,

diclofenac stimulated platelets but, probably precisely for this reason, could cause damage to the stomach mucosal circulation; bacterial peptides in high doses stimulated the vitality of leukocytes, but this could lead to an excess production of toxic oxygen radicals, etc.

Hormesis has had the great merit of disproving, with incontrovertible evidence, the belief that cause and effect must always be linearly related. This confutation of an old idea has, in its turn, provoked a domino-like collapse of many other mistaken theories, such as the claim of 'conventional' pharmacology that there must be a linear relation between the dose of a drug and its clinical effect. If hormesis were to be 'taken seriously' by the world of pharmacology, it would call into question the interpretation of pharmacokinetic curves: in fact, the concentration in the blood of any drug administered orally will be extremely low during its initial stages of absorption and in its final phases of excretion. During those times, if a hormetic phenomenon were to occur, the effect of the drug would be exactly the opposite of that intended. One strong indication that this is a very concrete possibility, even for very common drugs, is provided by the work of Doutremepuich et al. on aspirin.[9-14] It is worth mentioning, in this regard, that these authors observed the phenomenon of effect inversion with 'ultra low' doses and also with 'homeopathic' doses.

In thus confuting the accepted theories, hormesis reaches its peak of 'unconventionality' but also of 'scientificity', because science is 'strongest' precisely when it demonstrates – on the strength of evidence – that previously held views were limited or incorrect. Interestingly, at this stage of its development, the role of hormesis is historically comparable to the challenges levelled against conventional medicine by the homeopathic tradition.[15]

Homeopathy

Homeopathy is a method devised to find remedies for curing patients at a time (late 1700s, early 1800s) when therapeutic methods were only empirical and for the most part ineffective. The books on the history of medicine often neglect to mention that, in the historical period when it arose, homeopathy constituted the most 'scientific' pharmacological approach discovered until then, for the following reasons: (a) It was based on observations that were initially empirical, but which gave rise to a pharmacological theory (or rather, a general reference-principle): that of 'like cures like'; this principle, irrespective of whether or not it was correct, gave medicine a pharmacological theory to work out. (b) This general principle, which existed already in Hippocrates, became, after Hahnemann, a method for designing clinical tests on volunteers (relatives, students), which enormously expanded the body of knowledge of the 19th century pharmacopoeia; by way of example, we note that nitroglycerin was tested as a drug by Hering in 1849, while its use in allopathic medicine began some 30 years later.[16] (c) It was such tests, rather than abstract philosophical ideas, that revealed new properties of remedies in very low doses or even in high dilutions/dynamizations, thereby extending the possibilities for their use in hitherto undreamt range of dosages.

Homeopathy thus should have had no need to demonstrate its 'scientificity.' Yet, in practice, it ran into serious problems because the economic implications of the new discoveries, and a lack of 'diplomacy' on the part of Hahnemann, shifted the debate from the realm of scientific research to that of a power struggle, implicating the very survival of entire fields of medicine and pharmacy (see note 2). Unfortunately, even homeopathic practitioners themselves are not fully aware of the scientific basis of their discipline. The words and symbols ('similarity,' 'dynamization,' 'potency,' 'miasm,' 'vital force') have remained the same for 200 years, and homeopathic physicians have been 'content' with these original forms, which have always enabled them to survive and practice their profession. Another factor aiding the survival of homeopathy was that the competing fields of 'clinical' medicine did not have a great deal of scientific content at their disposal, and medicine had great difficulty (and still does) incorporating science into its conceptual arsenal.

Homeopathic medical science has never ceased constructing theories and working hypotheses about its basic principles, which are essentially three: the law of similia, the law of minimum dose and the 'holistic' treatment of the patient. These principles can in their turn be subdivided into many other points and sub-points, as typically occurs in any scientific theory: moving from the general to the particular.

The homeopathic 'simile'

To compare the fundamental principle of homeopathy with hormesis, we need to carefully define the working concepts. We agree with Calabrese and Jonas[1] in drawing a distinction between homeopathic 'similars'

and hormesis. In homeopathy, 'like cures like' essentially means that *a particular substance (in small doses or high dilutions, it doesn't matter here which) can cure a disease whose symptomatology in the patient is similar to that caused by the same substance in tests on healthy subjects*. This founding idea (theory) has been repeatedly tested in the experiments of homeopathic practitioners and has held up over time, albeit not in a sufficiently 'strong' manner to convince the entire world of medicine (see note 3).

The theory of homeopathic 'simile' is starting to be explained from a mechanistic standpoint, consistently with modern immunological and biological theories, with which it is partly in agreement and partly in opposition (as is also hormesis, in a different field). For example, today it is possible to explain – or very closely approach an explanation of – how a substance (e.g. bee poison) that causes pathological symptoms in healthy subjects (pain, inflammation) can cure similar pathological symptoms in subjects allergic to bee poison. The substance is administered sublingually to the allergic subject, in extremely small doses, and induces immunological tolerance by activating the counter-regulatory mechanisms of the lymphocytes. Much has also been written about so-called 'paradoxical pharmacology,' according to which it is possible to exploit the 'pathogenic' properties of drugs (determined from the pathological symptoms which they provoke in healthy subjects during phase 1 studies) for curing diseases that exhibit precisely those symptoms.[18-20] Though this is not overtly called 'homeopathy,' it is nevertheless, unintentionally, homeopathy: it is simply a question of agreeing on the words and symbols that are used.

It is also possible to design laboratory studies to test the following 'homeopathic' idea: a given substance causes an effect (for example stimulation) on resting cells or animals, but the same substance causes an opposite effect (for example inhibition) when tested on cells or animals that have been previously stressed or disturbed in some way. The idea – originally described as the 'Wilder rule' – has been tested in many studies of experimental physiology, cell biology and molecular biology.[21] Obviously, each individual model makes it possible to highlight a small aspect of such a general rule, thereby outlining some possible mechanisms. At the basis of the Wilder rule are the changes of receptors and of signal transduction pathways, caused by the pathology itself, which makes the stressed subject or system more sensitive and responsive to certain treatments and less so to others, even to the point of response inversion due to homeodynamic adaptations of the reactivity and/or of the effector systems, typical of living organisms. Another important mechanism that would explain the different actions on healthy subjects and patients is that the remedies may target only diseased tissues and not healthy tissues.[22]

Doses

The homeopathic Materia Medica includes many poisons and was compiled from observations of accidental poisoning cases or through experiments on volunteers. The latter, obviously, had to be conducted with doses capable of provoking 'symptoms' which, though disagreeable (but at times also agreeable, as can happen with some drugs), would not however cause serious damage to the subjects. So, it came naturally to reduce the doses to the minimum amount that was able to provoke symptoms (in the healthy subject) and to cure them (in the patient). It should be added that the effects of any drug are multifarious, so that when subjects are asked what symptoms they experienced after taking it, they will probably (or certainly, according to homeopathic experience) report effects involving many aspects of physiology and psychology. It is also likely that, as the dose is reduced and the most noticeable 'toxic' symptoms which affect all subjects are abated, other more specific symptoms, affecting more 'sensitive' subjects, may remain or even emerge. This is why the homeopathic Materia Medica comprises such a 'wealth' of symptoms, observed and meticulously described. We shall not debate here whether such methods are correct and statistically validated – a question not relevant for our present purposes, though it 'weighs' greatly on the quality of the medical prescriptions based on such reports.

Therefore, for what concerns dosages, it is obvious that overly high doses of any poison will have pathogenic effects, whereas low doses may have slightly pathogenic effects (liable to cause unpleasant symptoms) or pleasant or therapeutic effects, depending on the similitude we have discussed above. Certainly, this aspect has many conceptual analogies with hormesis. Nevertheless, we disagree with the general classification of these pharmacological effects as 'compensatory,' that is responses to damage induced by a high dose. In our view, the discussion on 'primary' (direct, stressful) and 'secondary' (indirect, compensatory) effects – introduced by Hahnemann himself to try to construct a theory of the remedy – is somewhat

contrived, and in any case unnecessary for clarifying the point of therapeutic effects of low doses of poisons. In practice, biological systems react in a unitary manner, so that these two types of effects of a remedy or toxic substance can only be artificially separated. To give a very simple example, consider the case of a single protein: if a chemical substance binds to an amino acid, the entire protein alters its secondary and tertiary folding or may form a complex with another protein etc. In this case, it is not possible to say whether the effect of the chemical substance is direct or indirect. Therefore, regardless of the theorized two types of actions of the remedy, the general working principle remains the same: use the lowest possible dosages, which appears to be in line with modern, intelligent pharmacology. The more 'specific' and 'targeted' a remedy is (i.e. directed to highly sensitive receiving systems), the lower will be its effective dose. A list of experiments where reproducible biological effects induced by compounds used in the concentration range of attomoles (10^{-18} moles/litre) or even zeptomoles (10^{-21} moles/litre) was previously reported.[23]

Dilutions/dynamizations (see note 4)

One fortunate circumstance for homeopathy, historically, was that although Avogadro's principle was formulated in the early decades of the 19th century, the precise computation of the number of molecules in a gram mole was published by Loschmidt only in 1865 (in fact today we speak of the Avogadro-Loschmidt constant). This meant that there was no 'scientific' objection to the use of ultra-diluted substances, and homeopathy was not theoretically destroyed, at least not in those years. The worst period came between the 19th and 20th centuries when, also thanks to the discovery of chemotherapeutics, homeopathy was brought to bay and reduced to a shadow of its former self. Today, in the computer era, we understand a great deal more about the physics of condensed matter and in particular of aqueous solutions containing gases, silica and ions (pure water does not exist), and this enables us to consider (at least as a hypothesis) various potential mechanisms by which 'non molecular' information might be incorporated into ultra-diluted solutions and transmitted to an organism.[24,25] We shall not here discuss this controversial question. However, to clarify the relation with hormesis, it is sufficient to note that many experiments conducted thus far on highly diluted solutions tend to show that the biological action of a given substance does not change direction when going from 'very low dose' to 'highly diluted-dynamized solution.' The most frequently described instance is the modulation of the function of basophil granulocytes by histamine, which is apparent both with low and unquestionably molecular dilutions (for example 2CH which corresponds to 10^{-4} moles/litre) and with high dilutions (for example 16CH which corresponds, theoretically, to 10^{-32} moles/litre).[26,27] The response of the living system to very high dilutions/dynamizations, when it can be observed, generally has the same direction as that to low (sub-toxic) dilutions containing ponderal, molecular doses of the substance to which the system itself is chemically sensitive. Considering histamine, the 'inversion of effects' may be conceived only by comparing the effect of this substance in the connective tissue (where at high doses it behaves as irritating, pro-inflammatory compound) with the effect on basophils (where it suppresses by internal feedback the release of histamine, thus behaving as anti-inflammatory compound). There are, however, discrepancies between different laboratories on this point regarding the inversion of biological effects in highly diluted solutions,[28-30] so that the question cannot be considered resolved.

We agree with Calabrese and Jonas[1] when they maintain that, in the 'high-dilution' field, it is difficult to find points of contact between homeopathy and hormesis: the 'classical' hormetic curves are in fact correctly and completely constructed only for 'doses,' – that is to say concentrations – from 'zero' (no effect, taken as control) upward, whereas homeopathy, as we have seen, also uses dilutions where theoretically there are no molecules of the purported active principles inside. In this second case, a 'common ground' between homeopathy and hormesis could be found only if we accept the possibility of 'supra-molecular' states of organization of the solvent, influencing the cell responses independently of the concentration of the solute. At present, this hypothesis is widely speculative, but we cannot rule out that studies based on the hormesis model may, in future, be extended to ultra-diluted solutions, should it become possible to determine the 'concentration' of any clusters, nanobubbles, nanoparticles or the like. Most probably, given that hormesis, too, is a phenomenon that seeks wider application in medicine, it would find fertile ground in the growing diffusion of homeopathy worldwide.

Conclusions

To conclude, is there space for hormesis within homeopathic theories? It would be helpful if this were true, because hormesis is a very robust phenomenon that also lends itself to formulating models and working hypotheses. Homeopathy has need for demonstrable facts and methodological rigour; it also needs to rid itself of the reputation of being unscientific. Calabrese and Jonas[1] suggest that 'certain forms of homeopathic treatment methods have the potential to be evaluated within the context of a post-conditioning hormesis treatment methodology, thereby permitting them to be rigorously evaluated within an experimental and detailed dose-response framework.' We fully concur with this view. If homeopathic remedies could be studied according to this approach (at least those made with low dilutions of substances), it would be a major step forward for homeopathy and medicine. This would however imply enormous research effort, because it would require plotting the dose-response curves of homeopathic remedies: first in pre-clinical studies (on animal models) and then on humans (first healthy volunteers and then patients), and in conditions under which sensitivity is highly likely to vary greatly between individuals (which would require using large groups of patients to obtain statistically valid results). It is therefore foreseeable that the points of contact between homeopathy and hormesis will, at least for some time, remain within the sphere of laboratory research – which in itself is already significant – though without ruling out more advanced forms of collaboration and the possibility of finding more concrete implications in medicine or of studying the mechanisms of actions of many other compounds or poisons.

In the final analysis, therefore: long live hormesis, and long live homeopathy, which are two different things but able to positively interact, as always happens when there is genuine scientific interest. We can find many points of contact because the reality is vaster than our symbols, and because our old and new words can proliferate and recombine to continually form new phrases. All this, bearing in mind that the ultimate aim of all efforts in medicine is, as written at the start of the Hahnemann's Organon, to care for patients and, where possible, to cure them.

Notes

1. Hormesis is a dose-response phenomenon characterized by a low-dose stimulation and a high-dose inhibition. More accurately, it is a dose-time-response relationship in which there is an initial dose-dependent toxicity response followed by a compensatory/rebound response, such that at low doses the response becomes greater than the original background state or control group value (Calabrese and Jonas[1]).
2. In this connection, we note that the battle is far from over, as we ourselves have sometimes experienced on sending rigorously scientific papers to pharmacology journals, with the response that they refused even to consider the work (that is to say not even submitting it for peer review), not because of any methodological objections, but merely because the subject was homeopathy. Homeopathy is still not considered a part of pharmacology, despite the fact that professional physicians prescribe homeopathic remedies and that these are purchased and used by the public: one example of how ideology (or economic interests) often stifles science and even common sense.
3. It should also be specified that the homeopathic pharmacopeia has, during the course of two centuries, spawned many diverse branches that include a purely 'clinical' use of the remedies: in short, if a remedy demonstrates therapeutic efficacy on a particular disease, it can be used again as a 'nosological' indication for that disease. In practice, this is very close to the concept of evidence-based medicine, even though the approaches suggested for proving homeopathy are often different from the conventional 'double-blinded randomized clinical trial.'[17]
4. Logically speaking, we can speak of a 'dose' of a given substance only when that substance is present and, therefore, when its concentration is higher than 10^{-24} moles/litre (approximate Avogadro limit). Beyond this limit, we can no longer speak of doses or concentrations, because a substance may not be present in an amount that is less than zero. That is why in homeopathy it is more correct to speak of 'dilutions/dynamizations,' which can be logically pushed beyond the Avogadro limit (corresponding to the 12th centesimal or 24th decimal dilution, starting from a solution of 1 mole/litre).

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