

# A scientific reappraisal of the 'principle of similarity'

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**Abstract** — In the history of therapeutics, the 'principle of similarity' — the treatment of 'same by same' or of 'like by like' — may be traced back to a number of medical traditions, including the systems of Hippocrates, Paracelsus and Hahnemann. Although in recent years we have witnessed a renaissance of interest in traditional medicines and 'holistic' medical practices, the reliability of the principle of similarity has still to be demonstrated on experimental grounds, and very few studies have been conducted to understand the underlying mechanism(s). Acceptance of this phenomenon requires supporting evidence of possible mechanisms and high-quality studies exploring its effectiveness in clinical medicine. The aim of this work is to provide a rational approach to the analysis of the various aspects of this historical yet also modern medical principle, in order to construct a plausible framework of ideas capable of facilitating further basic and clinical research into this field.

## A historical overview

The traditional application of the principle of similarity, also referred as 'similia principle', claims that when a substance is able to induce a series of symptoms in a healthy living system, it would be also able under certain circumstances to cure these symptoms when applied at low doses ('similia similibus curentur'). This empirical principle is deeply rooted in antiquity and has cropped up from time to time in different countries in the history of medicine (1). Primitive applications of the principle of similarity can be found in the magical practices of native peoples such as drinking decoctions prepared from the bodies of prolific animals (wasps, flies) in order

to cure sterility, ingesting the organs of slain enemies (cannibalism) in order to transfer bravery, or preparing aphrodisiac extracts from the testes-like orchid. Among the Greeks, Hippocrates (460–377 BC), who is considered the first representative of rational medicine in the western world, advanced a doctrine of similarity: 'Through the similar the disease develops and through the employment of the similar the disease is healed. So that which produces urinary tenesmus in the healthy, cures it in disease. Cough is provoked and healed through the same agent, just as in the case of urinary tenesmus' (2). The king Mithridates VI (132–63 BC) is reported to have taken small amounts of poisons and venoms to protect himself from repeated attempts at assassination by poisoning.

A more recent representative of this line of thought was P.T. von Hohenheim, also known as Paracelsus (1494–1541), who proposed the ‘doctrine of signatures’ (*signa naturae*), according to which the therapeutic properties of drugs could be deduced from observation of external features of plants or minerals: red drugs for hematopoietic diseases, sharply pointed leaves for stabbing pains, iris-like *Euphrasia* flower for eye diseases, and so on. The ‘magic simile’ (1) was thus used empirically for centuries without any scientific understanding or experimental proof.

The first serious and systematic utilization of the principle of similarity at the dawn of modern medicine dates back to the end of the eighteenth century, when the first vaccination procedures were attempted by pioneers like Jenner, Behring and Pasteur. However, it is clear that the use of a simile as a vaccine was designed right from the outset as a prophylactic method and not as a drug to be administered to people already affected by the disease. Only in the last few years has the utilization of molecular antigens as therapeutic agents been introduced in mainstream medicine (3–5).

The most evident and widespread utilization of the principle of similarity was carried out by homeopathy, a medical current founded by C.F.S. Hahnemann (1755–1843), which was very popular in the nineteenth century in Europe and the Americas, and subsequently declined to the point of almost total disappearance during the first half of the twentieth century. Two hundred years ago, the paper ‘Versuch über ein neues Prinzip zur Auffindung der Heilkräfte der Arzneisubstanzen’ (Essay on a new principle for ascertaining the curative powers of drugs), written by Hahnemann, was published in a German medical journal (6). This publication is considered by medical historians as the first in which Hahnemann’s system was enunciated in detail. A few citations from Hahnemann’s works may serve to introduce his view of the *similia* principle: ‘One imitates nature which at times heals one chronic disease by adding another to it and employs in the disease that drug which is in the position to excite another artificial disease as similar to it as possible and it will be healed: *similia similibus*’ (6); ‘By choosing a remedy for a given natural disease that is capable of producing a very similar artificial disease we shall be able to cure the most obstinate diseases’ (6); ‘Each individual case of disease is most surely, radically, rapidly and permanently annihilated and removed only by a medicine capable of producing (in the human system) in the most similar and complete manner the totality of its symptoms, which at the same time are stronger than the disease’ (7). Hahnemann also recommended the use of low doses and even of high dilutions (so

called ‘high potencies’) of drugs: ‘A medicine whose selection has been accurately homeopathic must be all the more salutary the more its dose is reduced to the degree of minuteness appropriate for a gentle remedial effect ...’ (7). This is a further, highly controversial, aspect of his medical system, but here we avoid the issue of homeopathic doses of drugs, which raises separate issues. Homeopathic historians have recognized that the most consistent contribution of Hahnemann was the *similia* principle and not the use of highly diluted compounds (1).

An interesting variant of the principle of similarity, mentioned even in the later editions of the Hahnemann book ‘*Organon of Medicine*’, is the so-called *isopathy*. The term was probably coined by the veterinarian W. Lux somewhere around 1831–1833 (8). He suggested that low doses of a contagious product (bacterium, virus or infected secretions, and organic material), after special preparation including sterilization, would exert a therapeutic action on the disease resulting from the contagion itself. The principle of similarity, *Similia similibus*, thus becomes: *Aequalia aequalibus*, or the principle of sameness. Many of the ancient authors in this field used in their therapeutics both *similia* and *aequalia* principles.

### Experimental studies

The old principle of similarity was formulated as a general ‘law’ on the basis of empirical evidence and analogical reasoning, but this kind of formulation does not allow any progress in the search for the possible mechanism of the alleged therapeutic effects. In current scientific literature, there is a substantial body of evidence and of examples that may provide new insights into the principle of similarity, not because it was formulated as a starting hypothesis or discussed as a possible related topic, but because these studies can document and clarify a number of specific aspects of the biochemical regulatory mechanisms that may underlie the observed paradoxical phenomena. Just to make a quantitative estimate, we performed a search in the international *Medline* database for the headings including the key words ‘paradoxical effects’, and we found that in the years from January 1994 to June 1996 the medical scientific papers referring to this topic have numbered 674.

Early attempts to investigate the principle of similarity on experimental grounds can be traced back to the years around the end of the nineteenth century, when H. Schulz published a series of papers that examined the activity of various kinds of poisons (iodine, bromine, mercuric chloride, arsenious acid, etc.) on yeast, showing that almost all these agents

have a slightly stimulatory effect on the yeast metabolism when given in low doses (9,10). He then came into contact with the psychiatrist R. Arndt and together they developed a principle that later became known as the 'Arndt-Schulz law', stating that weak stimuli slightly accelerate vital activity, medium strong stimuli raise it, strong ones suppress it, and very strong ones arrest it (11). Similar observations were reported by several other authors in the 1920s, and from their findings one can conclude that the phenomenon of inverse, or biphasic, effects of different doses of the same substance was well known before the era of molecular medicine (1,12).

The occurrence of dual effects (both stimulatory and inhibitory) caused by the same agent when used at different doses or for different times has been described in various experimental systems and has been often called 'hormologosis', or 'hormesis' (12-16). In 1960 Townsend and Luckey (13) surveyed the field of classic medical pharmacology for examples of hormetic effects and published a list of 100 substances known to be capable of causing an inhibition at high concentrations and stimulation at low concentrations. In general, such cases fell into three categories: those involving muscular response, those involving respiration, and those involving transmission of nerve impulses.

The similia principle has been investigated in a number of laboratory models. The most important data have been collected using models based on the activation of human basophils, lymphocytes, fibroblasts, renal cells, granulocytes, and vegetable cells. A review of the literature is beyond the scope of this paper, so we refer here only to a few representative studies and to some of our recent results. More detailed accounts have been reported elsewhere (17-19). An important series of experiments conducted by French groups were published in 1988 in a prestigious pharmacological journal, showing that very low doses of histamine and of an extract of honeybee (*Apis mellifica*) significantly inhibit basophil degranulation induced by anti-IgE antibodies (20). It is worth noting that both histamine and honeybee venom when delivered to a tissue at normal dosages have powerful pro-inflammatory irritant properties. Therefore, this experiment clearly illustrates the application of the principle of similarity in an experimental model: a substance that is known to stimulate inflammation at conventional doses, is able to inhibit the cell responsible for many phenomena of the acute inflammatory process. A similar approach was extensively adopted also by other groups, who reported the inhibitory effect of histamine on basophil activation (21,22).

We have developed various models where the

functional responses of human blood neutrophils are manipulated in vitro in order to express typical inversions of responses on varying the doses of the compounds. The first model showed that pre-treatment of neutrophils with low doses of the bacterial peptide fMLP increases their functional responsiveness to high doses (a phenomenon that we called *homologous priming*), while the pre-treatment with high doses of fMLP decreases their responsiveness to a second treatment with high doses (a typical example of stress-induced receptor down-regulation) (23). A second model showed that high doses of fMLP induce a marked increase of cell adhesion to serum-coated plastic surfaces; on the other hand, when the increased adhesion is induced by pre-treatment of neutrophils with the bacterial endotoxin (LPS), in these conditions a low dose of fMLP inhibits and reverses the LPS-induced adhesion (24). The phenomenon is not only present in LPS-treated cells, but we also described it in inflammatory cells, i.e. in cells that were harvested from an experimental inflammatory skin exudate (25). In conclusion, the chemotactic agent fMLP, which is considered to be an activator of neutrophil adhesion, paradoxically inhibits the same cell response at low doses when used in primed cells. We also investigated the mechanism of this phenomenon and found that low doses of fMLP stimulate an increase in cyclic AMP (cAMP) and that addition of cAMP plus theophylline to the LPS-treated neutrophils inhibits the adhesion. Therefore, it is highly conceivable that the phenomenon of inversion of effect in our model system — that is, the inhibition of cell adhesion caused by a cell agonist — is due to the increase in cAMP triggered by low doses of fMLP. The major role played by cAMP in the 'gating' of signal transduction pathways, and thus in the control of extent and direction (i.e. positive versus negative) of the response to a number of extracellular signals, has been recently reevaluated by others (26). A gating pathway can regulate information flow through the transmittal pathway positively or negatively and may be activated by intracellular or extracellular signals. Clearly this is only a representative of a number of possible explanations of apparently paradoxical phenomena that have been described in cell systems.

Toxicology research is a field where the low-dose reverse effects have been often described. Beneficial effects such as stress-induced proliferation are observed in cells exposed to low doses of toxins or of radiations (15-17,27-29). As regards the effects of radiations, the old tenet stating that cancer risk is proportional to dose has been recently challenged by data showing that cancer mortality in populations in higher natural background regions was lower than

that in populations living in low-background areas (30). This paradoxical phenomenon gives support to the concept of radiation hormesis, a beneficial effect of a low-level exposure to the same agent that is harmful at high levels. Diluted preparations of toxic compounds have been reported to increase the elimination kinetics of identical compounds and to protect animals (31–34), even if the number of methodologically sound, independently reproduced studies is too small to make any definitive conclusions (17).

As mentioned above, in the biomedical literature there are a number of reports about specific compounds that exhibit dual effects (positive and negative), according to different doses employed or to different conditions of testing. For example, these paradoxical effects have been reported using prostaglandins (35,36), amyloid  $\beta$ -protein (37), oxygen free radicals (38), nitric oxide (39), neuropeptides (40), cytokines (41), insulin (42), acetylcholine (43), and thrombin (44). We mention these findings essentially in order to draw attention to the complexity of these forms of regulation and to the existence of a subtle balance of opposite actions in all similar homeostatic systems composed by networks of multiple cell types and signals. This complexity is so great that some investigators have found it useful to apply mathematical models to the description of systems such as the immune network (45,46). These models have shown that effective regulation of the immune disorders can be accomplished with the same antigen or the same lymphocytes that are responsible for the induction of the disease, providing that the doses or the protocols of administration are changed.

Several animal models have revealed non-linear or even opposite responses to the same drugs or to immunoregulatory agents. By plotting the immune response to antigens in laboratory animals versus the doses of antigen used to pre-treat the animals, one can see that the immune response is depressed (state of *tolerance*) both in animals receiving very low doses and in animals receiving high doses of antigen. Intermediate doses, however, cause a greater response. A rat model was developed by our group, showing that injection of low doses immune adjuvant (based on killed *Mycobacterium butyricum*) into the peritoneum of rats is capable of preventing and curing the arthritis induced by the injection of high doses of the same adjuvant into the paw (47). This is a further example of the induction of tolerance with low doses of antigens, an immunomodulation procedure that has been extensively exploited in recent years in a number of conditions also in humans. We can only mention here a few examples of human therapies, which may be regarded as a special application of the 'simile' at the molecular level (3–5,48,49):

the use of bacterial endotoxins as immunostimulants, the treatment of immune disorders with immunoglobulins, of multiple sclerosis with oral myelin, of rheumatoid arthritis with oral collagen, of recurrent bronchitis with bacterial extracts, of allergic diseases with nasal allergens, of cancer with cancer vaccines made with tumor extract or tumor protein components, and of immune disorders with peptides binding to T-cell receptors or to HLA. Most of these therapies are still at the experimental stage, but their existence confirms the increasing popularity of the principle of similarity in modern medicine.

As regards the clinical research which is directly related to homeopathic treatment, we see that, notwithstanding the above-mentioned historical limitations, this field has slowly evolved and now things are changing, because modern medical methods (clinical trials, statistics, computer programs in reparameterization, laboratory studies) are being increasingly utilized. Clinical trials designed to investigate the efficacy of homeopathic treatment have often (but not always) yielded positive results. The authors of a meta-analysis of more than a hundred clinical trials in homeopathy (50) write: 'The evidence presented in this review would probably be sufficient for establishing homeopathy as a regular treatment for certain indications', even if they recommended more studies — and of better quality — before a definite conclusion could be reached. In a recent study published in the *Lancet*, it has been demonstrated that homeopathic immunotherapy is significantly ( $p = 0.003$ ) more effective than placebo in relieving the symptoms of bronchial asthma (51). Another randomized double-blind trial compared homeopathic treatment with placebo in the treatment of acute childhood diarrhea (52). An individualized homeopathic remedy (or placebo in the control group) was prescribed for each child in addition to the standard oral rehydration treatment. The results indicated that the treatment group had a statistically significant ( $p < 0.05$ ) decrease in duration and intensity of diarrhea with respect to the control group. These and similar reports stirred up considerable discussion regarding methodological aspects and interpretation of results. As a matter of facts, the above-mentioned trials and other clinical studies in homeopathy (50) are promising, but their clinical results, although significant, are tiny and need to be reproduced by independent groups before their claims could be universally accepted.

### A general model of the principle of similarity

The investigation of the scientific bases of the principle of similarity, at least as concerns its biological

applications, may be facilitated by the formulation of working hypotheses and rational models. To this purpose, we suggest that this principle, in its fundamental meaning, may be traced back to the principle of 'inversion of effects': *biologically active compounds may cause inverse or paradoxical effects on a complex homeostatic system when either the doses of the compound, or the methods of preparation and of administering, or the sensitivity of the target system are changed.* Such an expression of the principle of similarity can be used as an operative definition of an extensive series of biological phenomena ranging from the cellular to the clinical level, the common basis of which may be the versatile adaptability of living systems to external stresses.

Let us examine the main elements of this modern re-formulation of the similia principle. The *effects* that are observed or are expected to occur if the similia principle is operative (either in humans or in experimental systems) should be *inverse*, or *paradoxical*. This means that a compound (or a treatment) that — according to the current knowledge — is considered an inhibitor works as a stimulant, or vice versa a stimulant causes inhibitory effects. Stimulation and inhibition are the main end-point parameters that can be evaluated in almost all experimental settings: any compound or treatment can induce — directly or indirectly — quantitative and measurable changes of variables such as cell or population growth, body weight, heart rate, frequency of seizures, platelet aggregation, bleeding time, urine volume, etc. Recording of drug-induced stimulating and inhibiting effects and the construction of dose-response curves represent major tools of pharmacology because they are of fundamental importance for the characterization of the mechanism of action of any kind of drug.

According to our model, *inversion of effects* can be obtained by three fundamental ways: (a) by changing the *doses* of the compound or the duration of the application of the treatment; for example, high doses or long-lasting application may be inhibitory, low doses and short treatment may be stimulatory (as we will see later, also the opposite may be possible, according to the experimental systems employed); (b) by applying the same dose or the same treatment to a system that may present different *states of sensitivity* or of responsiveness; the same compound may cause stimulatory, growth-promoting effects on a healthy/unperturbed system and inhibitory, suppressing effects of the same variable when applied to the diseased/previously perturbed system; (c) by administering the same compound (or two similar compounds) through different ways; one way (e.g. parenteral injection) could cause activation or increased response, the other way (e.g. oral adminis-

tration) could cause suppression or tolerance (see also below).

A relevant point of the model concerns the concept of *sensitivity* of the system under treatment. Modern cell biology and immunology have shown that the sensitivity of biological systems (and of individuals) to a given treatment may vary considerably according to a number of factors ranging from genetic predisposition to environmental conditioning, and to previous experience (memory). The reasons for these behavior patterns of biological systems are complex, relating, as they do, to the modes whereby cells, tissues, and organs regulate the degree of sensitivity at receptor, biochemical, and genetic level. To cut a long story short, we can refer to the concepts of 'priming' and 'desensitization' (or adaptation). What is meant by *priming* is a state of hyperactivation in response to a given stimulant, which characterizes a cell after it has received pretreatment with low doses of the same stimulant (homologous priming) or of other stimulants of a different type (heterologous priming). The priming is due to exposure of new receptors, to activation of the same receptors and/or to a number of changes in the intracellular communication or enzyme systems. It is worth noting that priming has been described not only at the cell level, such as in leukocytes, but also in tissues and organs, such as in the airways of allergic individuals after repeated challenge with allergens (53).

What is meant by *desensitization* is a state characterized by lack of responsiveness to a given stimulus after the cell or the organism have received pretreatment with low, medium, or high doses of the same stimulant (homologous desensitization) or of different stimulants (heterologous desensitization). Generally speaking, desensitization (whether homologous or heterologous) may be due to many mechanisms, including shedding, down-regulation or inactivation of receptors, uncoupling of receptors from transduction systems, and de-activation of cell effector systems. A phenomenon similar to desensitization is *tolerance*, which can be defined as the acquisition of non-reactivity of the immune system to given antigens.

The sensitivity of the biological systems to endogenous and external regulators (including the drug) is therefore the product of a delicate and dynamic equilibrium, that can easily change due to the disease or to previous or concomitant challenge with other compounds. The alteration of physiological systems during disease predisposes them to changes in sensitivity at specific receptor levels, this being something with which classic pharmacology is also thoroughly familiar (54).

Another relevant aspect of the hypothesis involves the concept of the so-called *homeostasis*. A homeostatic system, in its essential make-up, consists in a *set of anatomical, biochemical, and functional elements designed to maintain a physiological variable within minimum and maximum oscillation limits*. Homeostatic systems are present at each level of biological organization: at *cell level*, (e.g. membrane transport systems, enzyme induction, heat-shock proteins, cyclic nucleotides), at *organ level* (e.g. regulation of blood flow, of numbers in cell populations, of structure and morphology), at *apparatus level* (e.g. regulation of blood pressure, thermoregulation, bowel function, sexual cycle, etc.), and at *superior function level* (e.g. mental and emotional functions, personality, character, decisions and frustrations, etc.). Most homeostatic systems are made by two or more sub-systems having opposite roles in the maintenance of the equilibrium. For example, the blood glucose concentration is regulated by hormones (insulin and glucagon) with opposite effects, the protein and nucleotide phosphorylation is regulated by enzymes (kinases and phosphatases) with opposite effects, the circulation is regulated by two systems (parasympathetic and sympathetic nervous systems) with opposite effects, the immune system is regulated by T helper and T suppressor cells (and, according to most recent views, by Th1 and Th2 cells), with opposing functions, and so on. In a number of circumstances, the relative activity of two or more of these sub-systems is dependent on the presence and concentration of specific regulatory substances.

The relationship between homeostasis and the similia principle is straightforward. In fact, the most reasonable explanation of the inversion of effects involves the presumption that the body (or the cell) tends to maintain a functional norm. Each living system is endowed with homeostatic systems that allow the action of a harmful agent to be counterbalanced by internal adaptation mechanisms. Reversible deviations from this norm tend to set into operation certain phenomena whose chief characteristic is re-establishment of the norm. When the concentration, the duration or the intensity of the stimulus are overwhelming, the system is severely damaged and eventually killed. However, it is possible that when the external stimulus is low and nontoxic, the living system is still sensitive to its presence and responds with activation of the homeostatic counterregulatory mechanisms, which, in turn, bring the system to a state of increased resistance and self-healing power. The similia principle presupposes that the intrinsic tendency to self-recovery can be supplemented and actively assisted by the employment of suitable stimuli.

Since there are various possibilities for the inversion of effects and there are a number of experimental models at cellular and at systemic levels where these phenomena can be documented, there is not a single mechanism that can explain every possibility. However, an unifying general idea that may underlie any specific model could be found in the *biological complexity* (also, the concepts of complexity is incorporated in the above-reported definition of the similia principle). In recent years the awareness of the complexity of living systems and of their pathological modifications represented by modern diseases is increasing: in brief, a system can be defined as a 'complex system' not only when it is made of many different components, but specifically when these components interact, so that the whole is more than the sum of its parts (55). The whole body can be seen as a complex homeostatic system. Of course, the more complex the system, the more complex must be the control networks responsible for guaranteeing effective communications and specific responses. The study of complex systems (55–58) has shown that they exhibit peculiar properties, such as non-linearity of dose-effect relationships, plasticity and memory of past experience (priming, desensitization, conditioning), sensitivity to minor perturbations, network organization of signaling pathways that form multiple homeostatic feed-back loops, dynamic oscillations of physiological variables over time.

All these properties may be summed up in the sophisticated 'action–reaction' principle that governs homeostasis: the body (and the cell) does not behave simply passively but also actively, and the phenomena following challenge with external stresses are both passive ('suffering') and active ('reactive'), which serve as defense against the damage. In an ideal therapy, the first must be attacked and blocked, the latter must be supported; no single therapeutic tenet is sufficiently broad to embrace the infinitely variable and composite phenomena of disease.

The general hypothesis that we propose here is that these peculiar properties of living systems may represent the physiological basis of the principle of similarity. In a schematic and simplified way, the hypothesis can be summarized as follow.

1. A homeostatic complex system is endowed with regulatory systems (receptors, transduction and effector mechanisms) that may have opposite functions (for sake of simplicity, stimulatory or inhibitory). It is possible that under particular circumstances, different doses of the same compound activate either the stimulatory or the inhibitory pathways. This is the most simple case

- of inversion of effects, that can be documented by non-linear dose–response curves.
2. Considering the perturbed system (or the diseased animal or the patient in the case of the clinical applications of the principle), this is a system whose self-recovery mechanisms work at a sub-optimal level due to the continuous stress or to insufficient adaptive responses. One can assume that under particular circumstances its sensitivity to external regulation is profoundly affected by the disease itself. For example, it is highly conceivable that certain sensitivities are accentuated (primed), while other sensitivities, particularly after repeated specific challenge of the same receptors, are decreased or even absent. It is possible that a compound that has little or no effect on a healthy system proves to have high and specific (low-dose) effects on a sick, primed, system. Conversely, it is also possible that a different compound, whose action on a healthy system appears as a stimulation, has no effect or has an opposite effect on a diseased system. In this case, the inversion of equilibrium of the two opposing homeostatic subsystems whose existence is postulated as in the previous point.
  3. The last question is whether these concepts can be extended to the ‘classic’ similia principle, that was founded on ‘symptom similarity’. This is the most controversial point because the analysis of symptoms does not appear to be as ‘scientific’ as the objective measurement of some physiological or biochemical parameter. The use of symptoms as the basis for the choice of remedy appears to be in contradiction with modern scientific medicine, which demands explanations at the biochemical and molecular level. However, we suggest that this contradiction is more apparent than substantial. In fact, each symptom can be regarded as the expression of a series of biochemical and pathophysiological modifications which often may be identified: high temperature may be an expression of the reaction of the thermoregulatory center to the cytokines produced by activated inflammatory cells; skin redness may be an expression of the local reaction of smooth muscle and endothelial cells to several inflammatory mediators, including histamine produced by activated basophils and mast cells; anxiety may be an expression of the central effect of a number of endogenously generated molecules including catecholamines produced by the sympathetic nervous system as a reaction to stress; desire for salt may be an expression of the reaction of the hypothalamus to the imbalance of electrolytes

caused by retention of water, and so on. If this is true, in clinical activity, both noting symptoms and measuring hormone levels are informative for the physician. What changes is the level of integration of all the information that these different diagnostic procedures can provide. Therefore, according to the traditional similia principle, a drug that in a healthy and sensitive subject is capable of causing the expression of a certain pattern of modifications (symptoms), could be capable of inhibiting the same or ‘similar’ modifications when they develop during a disease. This may occur because, when a drug is capable of inducing in a healthy subject similar symptoms to those produced by the disease, the same drug would be expected to ‘touch’ the same or similar regulatory mechanisms inside the body that are affected by the disease. The ‘diseased’ homeostatic systems are expected to respond to the same drug with an opposite reaction, and thus to help the healing process. In synthesis, we suggest that careful analysis of clinical signs and symptoms according to traditional Hahnemann’s procedure could enable the physician to achieve different, but not contrasting, levels of understanding the pharmacological properties of biologically active compounds and possibly of manipulating the complex and subtle pathophysiological disorders that have part in the disease. Obviously, such procedure would raise a whole series of new questions, the two main issues being the reliability of the experimental ‘provings’ of remedies in healthy subjects and the problem of the doses to be administered to patients.

### Conclusions and prospects

The studies referred to here indicate that the above-presented models of the inversion of effects in biological systems are consistent with a large series of experimental data emerging from various fields of modern biomedical research. Nobody can deny that most pharmacological and toxicological effects follow typical dose–response sigmoidal curves. On the other hand, there are a number of exceptions to this rule, showing that the effect of a certain compound can be either positive (e.g. stimulating or priming) or negative (e.g. inhibiting or blocking) depending on the doses employed and on the conditions of the treated system.

Hormetic effects may have a number of explanations at the level of receptors, signal transduction mechanisms, enzyme regulation, and gene expression, according to the test compound and system involved

(12–16). Irrespective of the mechanism, common denominators evidently exist in the thresholds of perception and levels of response of organisms to drugs and/or toxic substances. If we assume that the response of a cell involves one or more molecular modifications and biochemical reactions, the lowest possible reaction, occurring just above the sensing threshold, is an apparent overcompensation to the potentially harmful changes that may be caused by medium/high doses of the same compound. These phenomena are reminiscent of the above-mentioned ‘Arndt–Schulz law’ and could be regarded as an application of the principle of similarity in biological systems when they are exposed to specific experimental conditions. However, this is only a general indication, because the clarification of the mechanisms(s) underlying most of the paradoxical effects reported requires further investigation. Moreover, the clinical evidence of the application of the ‘classical’, symptom-based, similia principle is still provisional and uncertain.

In any case, this study shows that the ‘similia’ concept is a topical question: several reasons suggest that the scientific re-evaluation of the principle of similarity is worthy of increasing attention. The first reason is that this concept may represent a broad unifying frame of reference for theoretical models explaining both a body of empirical observations emerging from old medical literature and the increasing experimental evidence of paradoxical results or of apparently opposite results described by different investigators in fields ranging from molecular biology to immunology and neurobiology. If this general frame of reference gains credibility and is increasingly documented experimentally, some apparent contrasts between empirical medical approaches and mainstream medicine approaches could be reconciled in a rational way.

The second reason why a reappraisal of the principle of similarity appears to be worthy of attention is that it can be used as a ‘heuristic principle’: that is, a driving force on the basis of which new experimental ideas are generated in intellectually curious medical investigators. Every investigator dealing with a specific field could design new experiments based on the principle of similarity. A knowledge of the principle of similarity/inverse-effects phenomena should encourage a positive and fruitful reappraisal of certain experimental results that may appear at variance with or even opposed to the starting hypothesis. Finding unexpected, controversial, and paradoxical results is a common experience in science, but often these results are ignored and discarded because they do not fit the main theories. The occurrence of inverse effects according to the general principle of

similarity could help and stimulate scientists to subject these data to a positive re-think: they will appear as an expression of the self-recovery phenomena which are typical of complex biological systems.

Third, the recognition of low-dose beneficial effects of toxic compounds and radiations may have an impact on the determination of optimal exposure levels for environmental agents to which a population is exposed. On the basis of the above-reported evidence, it is conceivable that rigid risk assessment, based on a linear model, should be substituted in many circumstances by a more pragmatic judgmental approach, based on accurate weighing of the epidemiological and experimental evidence on the effects of specific compounds in a given area. It has been shown that, if hormesis occurs, the standard logistic model for the determination of EC50 (the concentration or dose which gives a 50% effect) and of confidence intervals does not fit and should be extended and reparameterized (59,60).

Finally, the principle of similarity could be re-evaluated as a way of designing therapeutic strategies, according to two main lines, i.e. either by administering the ‘simile’ as a substance belonging to a known pathogenetic mechanism of the disease or administering the ‘simile’ as a compound that causes similar symptoms. The first line corresponds to the approach which historically has been called ‘isopathy’ or ‘therapy by nosodes’ and whose current up-dating consists in the utilization of a series of agents that are pathogenic when used at high doses in healthy people and therapeutic when used at low doses in sick people: cytokines, bacterial products, specific antigens, nitric oxide, cancer cells modified by genetic engineering, etc. The second possible line of therapeutic exploitation of the principle of similarity is based essentially on symptom similarity and has been pursued, to date, only by the classic homeopathic school. A critical point of the application of any therapeutical procedure exclusively based on symptoms is that in many diseases these are vague, unreliable and even ambiguous, and thus also the effect of remedies prescribed according to them would be unpredictable. On the other hand, in the classical homeopathic procedure, the emphasis is not directed to a single symptom or to a few symptoms, but to the totality of symptoms, i.e. to the entire pattern of characteristic symptoms that define a sick person. Therefore, it is possible that the lack of specificity of a symptom would be compensated, at least in part, by the accurate evaluation of a number of symptoms and by the definition of a typical portrait of each patient (so called ‘individualization of cure’). Only well-conducted and statistically sound clinical research can validate or contradict this hypothesis.



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