British Homoeopathic Journal
April 1997, Vol. **86**, pp. 73–85

The similia principle

From cellular models to regulation of homeostasis

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Abstract
We have developed two models of the similarity principle, essentially based on the regulatory mechanisms of biological homeostasis. A first model (gating theory) is designed to explain a series of experimental findings obtained in our laboratory, pointing to the occurrence of inverse effects of various agents on human neutrophils *in vitro*. A second, more general, model (regulation of stressed homeostatic networks) is designed to integrate modern concepts of priming, desensitization and signal transduction into the classical homoeopathic theory of inversion of effect at the clinical level, i.e. the symptom-based similia principle.

KEYWORDS: Similia principle; Homeostasis; Leukocytes; Receptors; Transduction systems; Gating theory; Stress; Inverse effects; Hormesis.

Introduction

Experimental papers reviewed by Bellavite and Signorini[1] have shown that homoeopathic treatment can be investigated using up-to-date scientific methods, but the physiopathological mechanisms and pharmacodynamic principles underlying the clinical effects of homoeopathic medicines await further clarification.

The basis of homoeopathy is the similia or similarity principle. It can be formulated as follows.

—Every biologically active substance (drug, toxic compound, bacterial product, plant extract, etc.) produces characteristic symptoms in healthy bodies which are susceptible to being in some way disturbed by that substance.
—Every sick body exhibits a series of characteristic symptoms typical of pathological change in that particular subject.
—The healing of a sick body may be achieved by targeted administration of the drug which produces a similar symptom picture in healthy bodies.

This principle was formulated as a general law on the basis of empirical evidence and analogical reasoning (*similia similibus curentur*) and consolidated over 2 centuries of homoeopathic proving procedures and clinical results. On the other hand, understanding the physiopathological mechanisms of the paradoxical healing effects of toxic compounds requires the development of models that could be experimentally tested on cellular and animal systems.

The similarity principle is not the only one in homoeopathy. Hahnemann also recommended the use of low doses and even of high dilutions/dynamizations (high potencies). We do not intend to deal with the problem of dilution/dynamization here, but will focus attention on the possible biological basis of the similarity principle. This may be investigated and understood as a distinct issue with respect to 'high dilution' or 'high potency' effects for several reasons.

—Historically, the similarity principle is the first law and the basis of the homoeopathic method.
—Most homoeopathic drugs on the market contain significant amounts of active compounds and their action could be interpreted on the conventional molecular paradigm.
—In cellular models and in animals, the similarity principle can be found to be operative also when using low to medium doses of biological compounds, though several laboratories have also described biological effects with highly diluted/ succussed solutions.[2]

Investigation of the scientific basis of the

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similarity principle, at least in its biological applications, may be facilitated by means of working hypotheses and rational models. We suggest that this principle, in its fundamental meaning, may be traced back to the principle of 'inversion of effect':

> Biologically active compounds may evoke inverse or paradoxical effects in a complex homeostatic system when the dose of the compound, the method of preparation and exhibition or the sensitivity of the target system are changed.

In these terms, the similarity principle may serve 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 versatile adaptability of living systems to external stresses.

Stimulatory effects due to toxic agents used in low doses or for short periods have been described in various experimental systems and are often called hormoligosis, or hormesis.[3-7] In 1960 Townsend and Luckey[4] surveyed the field of classic medical pharmacology for examples of hormetic effects and published a list of 100 substances known to cause inhibition in high concentrations and stimulation in low concentrations. In general, such substances fell into 3 categories, those involving muscular response, respiration or transmission of nerve impulses. Hormesis is thus a special application of the similia principle at the biological and physiopathological level but is not 'the' explanation of the similia principle, which may have further and more complex implications at the level of the whole human organism. Moreover, as we will show in this paper, there are other inversion of effect phenomena where low doses have inhibitory effects, while high doses of the same compound are stimulatory. These phenomena should have different explanations with respect to classical hormetic effects.

Experimental findings of priming and inverse effects

In this section we report experimental data pointing to changes in response and leukocyte sensitivity under conditions of stress caused by adding various compounds for which these cells have specific receptors. Although related to particular experimental models, our studies help to explain some general aspects of the complex regulation of biological systems (priming, desensitization, non-linear responses) and anticipate some concepts we shall utilize for the construction of a more general model of action of homoeopathic medicines.

Investigation of multiple responses of neutrophils to bacterial products[8] has shown that adding a high dose of the bacterial peptide fMLP to cells in culture (e.g. 100 nM or 1,000 nM) induces a rapid response in terms of superoxide production. The cells no longer respond if the same high dose is repeated after 10 minutes, having lost sensitivity to the stimulant in a phenomenon called desensitization. Moreover, a low dose of fMLP (e.g. 1 nM) does not cause superoxide response of neutrophils. Addition of a higher dose (e.g. 100 nM) to the cell incubation mixture after 10 minutes will, however, elicit a marked response (increased superoxide production), much greater than the response of control cells treated with a high dose but not given low-dose priming. The experiment showed that a low dose sensitized cells to a high dose, making them more responsive, and this is exactly what we mean by the term priming or, more precisely, as it is due to the same substance, homologous priming.

Homologous priming is associated with an increase in membrane receptors for fMLP and other stimulants, desensitization with a marked decrease in membrane receptors for fMLP. However, it should be pointed out that desensitization is stimulant-specific. Cells treated with either low or high doses of fMLP are normally still responsive or even primed to other stimulants like opsonized yeast, lectins or phorbol esters. On the other hand, after pre-treatment with either low or high doses of bacterial endotoxin (*E. coli* lipopolysaccharide, LPS), the cells are primed for enhanced response to fMLP. These important physiopathological modifications of cell receptors are called heterologous priming. We and others described these phenomena both in cell culture and in *'in vivo'* inflammatory models.[9] Leukocytes harvested from inflammatory exudates exhibit profound modification of sensitivity to specific factors, with increased response to fMLP and substance P, normal response to opsonized yeast, and low, down-regulated response to tumour necrosis factor α.[9] These data are summarized in Table 1.

We observed typical inversion of effects

Cell pre-treatment	Stimulant used	Effect of pre-treatment*
Low dose fMLP	High dose fMLP	↑(= homologous priming)
High dose fMLP	High dose fMLP	↓(= homologous desensitization)
Low/high dose LPS	High dose fMLP	↑(= heterologous priming)
Low/high dose fMLP	High dose phorbol esters	↑(= heterologous priming)
Inflammation	High dose fMLP High dose substance P	↑(= heterologous priming)
Inflammation	High dose opsonized yeast	— (= normal response)
Inflammation	High dose TNF-α	↓(= cellular stress-induced desensitization)

TABLE 1. Regulation of superoxide production in human neutrophils.
* The effect of the *in vitro* pretreatment was evaluated by comparing the superoxide production by neutrophils stimulated after the indicated pre-treatment with production by neutrophils stimulated without pretreatment.[8] The effect of inflammation was evaluated by comparing the superoxide production by neutrophils harvested from a skin experimental inflammatory exudate with the production by neutrophils isolated from peripheral blood.[9]
↑ = enhancement, ↓ = decrease in production.

Tested function	Low doses fMLP (1–10 nmol/l)	High doses fMLP (100–10,000 nmol/l)
Superoxide production (8)	— (priming only)	↑
Adhesion (normal cells) (10)	— (= no effect)	↑
Adhesion (LPS-primed cells) (10)	↓	↑
Adhesion (*ex vivo*-primed cells) (11)	↓	↑
fMLP receptor expression (8, 12)	↑	↓
Cytosolic [Ca^{++}] (8)	↑	↑
Cytosolic [cAMP] (10)	↑	↑

TABLE 2. Dose-dependence of various functional responses of human neutrophils to bacterial peptides (fMLP). The results are summarized from the papers quoted in parentheses.
↑ = enhancement, ↓ = decrease.

on the adhesion of human neutrophils with different doses of fMLP.[10] We studied adhesion responses to fMLP of neutrophils treated with bacterial endotoxin (lipopolysaccharide, LPS). Investigating the dose-response relationships of the adhesion response in these cells, we noted an unexpected phenomenon:

—In control cells, doses of fMLP higher than 50 nM stimulate adhesion, as expected and described in the literature.
—Using LPS-treated cells we noted that priming augments cell adhesion in the absence of further stimulation.
—High fMLP doses (> 50 nM) increase adhesion and are additive to the spontaneous adhesion induced by priming.
—In LPS-treated cells, addition of low, substimulatory doses of fMLP (0.5–5 nM) inhibits and reverses spontaneous adhesion. The chemotactic agent fMLP, considered to be an activator of neutrophil adhesion, thus paradoxically inhibits the same cell response when used in primed cells in low doses.

Reversal of adhesion by low doses of fMLP was detectable not only in LPS-treated cells, but also in tumour necrosis factor (TNF-α)-treated and inflammatory cells, i.e. in neutrophils harvested from an experimental inflammatory skin exudate.[11] This indicates that it is not a laboratory artefact but plays a physiological role in leukocyte kinetics and distribution of the cells inside the body.

We also found that low doses of fMLP induce rapid actin polymerization at cytoskeleton level and a variety of intracellular modifications at signal transduction pathway

level, e.g. increase in cyclic AMP (cAMP) and free calcium (Ca^{++}). The dose-dependence, including inverse effects, of several cell functions taken into consideration in our studies is shown in Table 2.

We recently investigated the *in vitro* effects of a potentized drug derived from an extract of *Podophyllum peltatum*.[13] Human neutrophils pre-treated with low potencies (4x) of this drug (final concentration of active ingredient 0.025 µg/ml), gave an enhanced oxidative response to subsequent challenge with bacterial formyl peptides. This priming effect was reproduced with purified podophyllotoxin in doses of 0.1–10 µg/ml. On the other hand, doses of pure podophyllotoxin greater than 100 µg/ml inhibited the response, so that the dose-effect curve of the pure toxin showed a typical reverse U shape. The same toxin thus causes enhancement of oxidative metabolism at low doses and inhibition at high doses. It is worth noting that high dilutions of *Podophyllum* produced only the priming effect on oxidative metabolism typical of low doses of pure toxin.

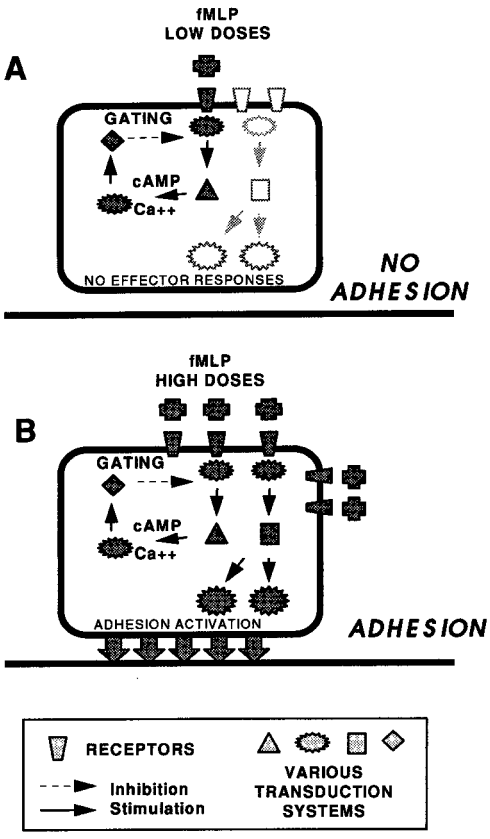

FIGURE 1. Schematic representation of the main modifications of a neutrophil treated with low (A) and high (B) doses of fMLP.

In all these experiments, dilution was followed by intense shaking, but in our experimental conditions we found significant and highly reproducible effects on cell functions only with low doses of active compounds, and not with so-called 'high dilutions' (beyond Avogadro's number). Our models thus involved 'classical' regulation feedback based on molecular, cellular and biochemical interactions. In previous experiments,[14] we described an inhibitory effect of high potencies (beyond Avogadro's number) of *Phosphorus* and *Magnesium phosphoricum* on neutrophil oxidative metabolism, but these effects were not registered with all the cell preparations, making a reproducible and reliable assessment of biological phenomena very difficult.

Gating theory

The above data raise a number of questions concerning the mechanisms of these effects, the main problem to be addressed being how a well-known stimulant of adhesion (the bacterial peptide fMLP) can become an inhibitor of adhesion with LPS-treated cells. We call the model we propose 'gating theory'. The gating concept means that some signals have a controlling function in the signal transmission sequence inside the cell—gating—that may enhance or block other signals. The major role played by intracellular messengers such as cAMP in the 'gating' of signal transduction pathways, e.g. in the control of extent and direction (positive versus negative) of the response to a number of extracellular signals, has been recently re-evaluated.[15]

It is of course worth noting once again that this does not explain the therapeutic effects of potentized drugs, but provides a precise experimental model for showing how the homoeopathic similia principle can be explained at cellular level. Our experiments do not explain the 'general' effect of high potencies on the whole organism, but it is conceivable that there are homoeopathic

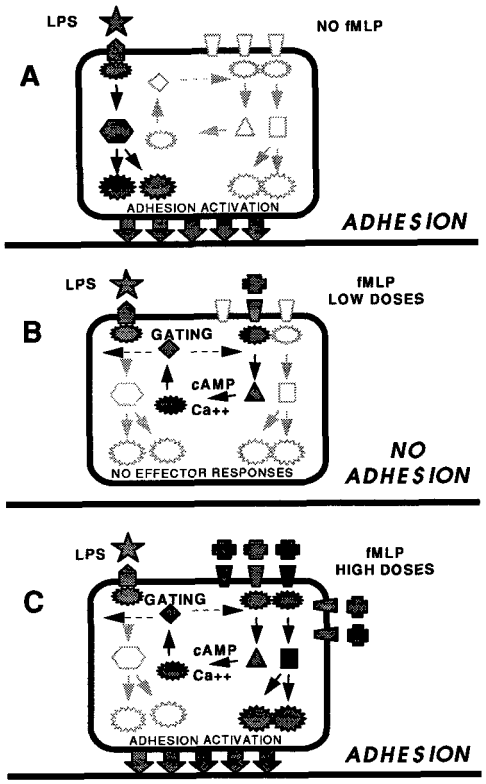

FIGURE 2. Model of inverse effect of fMLP on neutrophil adhesion. In the presence of LPS cells adhere in the absence of fMLP (A). Addition of low doses of fMLP triggers the gating pathway that inhibits adhesion (B). High doses of fMLP trigger both the gating and other transduction pathways different from those of low doses that bypass the gating mechanism and induce adhesion (C). Further explanations in the text.

medicines that act according to this model, among them low-potency extracts or self-derived products (hormones, cytokines, organ extracts, antigens, etc.).

Figure 1 shows a schematic representation of a cell treated with low (A) and high (B) doses of fMLP. Low doses do not stimulate adhesion but they stimulate an increase in intracellular cAMP by activation of the enzyme adenylate cyclase (triangles in Figure 1). cAMP is known to be an intracellular messenger for many enzymes, one of them protein kinase A. Activated protein kinase A is in turn able to inhibit part of the very complex transduction mechanism of the fMLP receptor, probably phospholipase C, by phosphorylation. We call this a gating pathway. To get full activation (Figure 1B), fMLP in high doses uses a different transduction pathway (probably the massive phospholipid breakdown with generation of a number of other messengers such as arachidonic acid, phosphatidic acid, lisophospholipids, diacylglycerols, etc., represented by squares in Figure 1), and so by-passes the inhibition by cAMP at least in part. The increase in cAMP is a signal functionally opposite to the effect of high doses fMLP, thus creating a kind of homeostatic balance, a kind of 'brake' that prevents a harmful overactivation.

Figure 2 shows the same system in the presence of LPS. LPS treatment alone (without fMLP) triggers adhesion of a substantial number of cells (Figure 2A). Under these conditions of increased adhesion, fMLP (low doses) works as an inhibitory signal, a 'brake' that inhibits and reverses adhesion (2B). In the presence of high fMLP doses (2C), on the other hand, inhibition is by-passed by different, cAMP-insensitive pathways and adhesion is activated. This may be the mechanism of bi-phasic, non linear dose-dependence of adhesion with respect to fMLP doses seen in the experiments.

Let us draw an analogy with the homoeopathic similia principle. LPS-treated cells represent the 'disease' of the leukocyte *in vitro* system, assuming that bacterial LPS mimics the pathological condition. Addition of fMLP represents the therapeutic 'simile', because this agent causes 'similar' pathological effects (adhesion) when tested in high doses in a healthy system (Figure 1) and therapeutic effects (inhibition of adhesion) when tested in a sick (LPS-treated) system (Figure 2).

The model, with cyclic AMP as a gating mechanism allows a prediction to be made. If it is correct, we should inhibit adhesion of LPS, even in the absence of fMLP, by increasing cellular cyclic AMP. cAMP can be increased in a number of ways. We used a system based on addition of dibutirryl cAMP. This enters into the cell releasing cAMP plus theophylline, blocking the enzymes that destroy cyclic AMP. We have therefore done an experiment, the results of which are in agreement with the theory that the addition of theophylline plus dibutirryl cAMP inhibits adhesion (unpublished results). We also

found that low doses of other stimulants, such as phorbol esters, which do not increase cAMP levels, do not inhibit but stimulate adhesion.[10, 11] It is therefore conceivable that inversion of effect, that is, inhibition of adhesion, is due to the increase in cAMP caused by low doses of fMLP, even if we can not exclude other mechanisms. In other words, cAMP is a negative signal responsible for inhibition of adhesion.

In our experience, opposite effects of the same agent can be observed in several models (see Tables 1 and 2), but the experimental conditions (doses, type of stimulant, cell treatment, cell function) must be carefully chosen in order to regulate the complex balance of receptors and transduction mechanisms. These phenomena at cellular level should thus be regarded not as a 'universal law' but an expression of possible behaviour in a living system under suitable conditions.

The gating theory is not the only model that can explain the occurrence of inverse effects at cellular level. One should consider, for example, the presence of receptors with different affinities and different coupling to effector systems, or the induction of detoxification enzymes (gene expression and enzyme activation). Other authors, in particular Van Wijk et al.[16] and Oberbaum and Cambar[3] have put forward different theories based on heat-shock proteins and hormesis models. These theories do not conflict, but concern different levels of cell organization. The model based on gating by cAMP helps to explain experiments showing inverse effects of biological compounds which are not toxic, but have regulatory properties through their action on receptors and transduction systems. The heat-shock protein model helps to explain experiments where the investigators have used extremely small doses of toxic compounds such as arsenic, cadmium, mercury to protect cells (renal cells, lymphocytes) from intoxication.

Regulation of stressed homeostatic networks

A large body of experimental evidence obtained in cellular systems thus points to the existence of a general principle of inversion of effect and non-linear dose-response relationships. This phenomenon occurs in issues raised in homoeopathy and is connected with the explanation of the similia principle, at least at the biochemical and cell biology level. The principle of similarity enunciated by Hahnemann is clearly based on *symptom* similarity and we will see that it finds its justification in the complexity of homeostatic control and in sensitivity of the human organism. At the level of simpler systems the same principle may be expressed as paradoxical reactivity to experimental stimuli and changes in specific biochemical variables. As it is conceivable that homeostatic systems at various levels are organized in hierarchies of regulatory mechanisms and that multiple communications exist between the different levels, it is also conceivable that the elucidation of the mechanisms of inverse effects at cellular level may be central to the understanding of the similia principle at a more general level.

Non-linear dose-response curves are widespread in biology and pathology and especially in immunology and neurobiology. The phenomena of priming, desensitization and inverse effect have also been described in many other situations in different cell types, tissues and whole organisms. An example of tissue priming is enhanced bronchial reactivity in asthmatics; of organ priming athlete's heart; of system priming nervous and immune hypersensitivity after challenge with sensory stimuli and antigens respectively.

Here we present a general model of the similia principle that incorporates both the biological concepts discussed above and the great importance of symptom analysis as proposed by the classical homoeopathic theory. The model was described in our recent book,[1] and is here presented with some updating. We called this model 'regulation of stressed homeostatic networks' because it basically concerns the reaction of homeostatic networks to stress and the possible role of homoeopathic regulation of self-recovery.

Homeostasis

The concept of homeostasis, introduced by W. B. Cannon in 1935,[17] refers to all activities that tend to keep the variables of a vital system constant, or, to be more precise, within acceptable limits. Hahnemann must also be mentioned in this context, because he founded his medical system on the principle of action/reaction. He outlined this fundamental principle in § 63 of the *Organon*:

> Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or shorter period. This is termed primary action. To its action our vital force endeavours to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of secondary action or counteraction

It may be useful here to take a look at the homeostatic concept in detail, using a schematic model of the type illustrated in Figure 3A. A homeostatic system essentially consists in a set

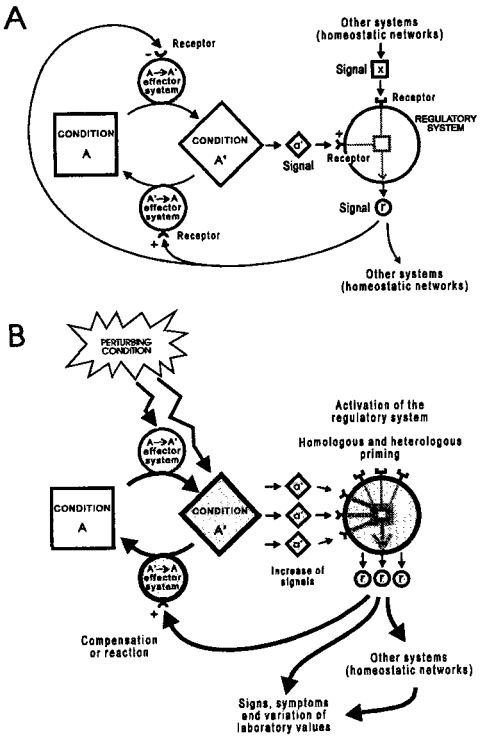

FIGURE 3. Schematic representation of a typical homeostatic system (A) and its modifications under stress (B). The perturbing condition is posited as being that which acts on the effector system $A \rightarrow A'$ or directly upon A', leading to an excessive increase in that parameter. With an increase in signal a', the regulatory system is activated and reacts by attempting to restore the lost equilibrium.
+ = stimulatory effect; - = inhibitory effect.

of anatomical, biochemical, and functional elements designed to maintain a physiological variable within minimum and maximum oscillation limits. Let us consider a variable A–A', which is in a state of imbalance and reversible due to the action of two operator or effector mechanisms, which may take A to the A' level or condition and vice versa. The system cannot function properly without some form of control, which is provided by a regulation centre(s) which receive(s) information from A' in the form of a signal a' associated with its condition (for example, an enzyme reaction product proportional to how much of A' is present or how much of A' is functioning). When the signal a' increases, the regulation system is activated and produces the signal r, which then inhibits the $A \rightarrow A'$ mechanism and/or activates the $A' \rightarrow A$ mechanism. These effector mechanisms (enzymes, membrane pumps and channels, also antibodies or cells of various types, according to the systems considered) usually have incorporated receptor sites for regulatory signals. The homeostatic system thus consists of feedback loops by which information on the outcome of a transformation or activity oscillation is communicated in revised form to the entry point of the cycle. The essential constituents of homeostatic biological systems are:

—*anatomical or biochemical structures* with adjustable and reversible effector functions
—*signal molecules* which enable nearby and remote structures to communicate
—*receptors* for signal molecules or other types of messengers with specific affinity capable of transmitting the signal to other elements of the regulation system
—*transduction systems* coupling receptor activation with production of signals or activation of effector mechanisms
—*elements responsible for information storage* for a given time period.

The model in Figure 3A also considers the fact that the various elements of the system relate to other systems. Signals a' and r may have effects on other control systems and effector mechanisms, and the regulatory system may have receptors for other signals and be influenced by these. As a general rule, therefore, homeostatic systems are networks of many elements.

The model in Figure 3A is therefore an over-simplification of physiological reality,

representing only the core structure of biological homeostatic systems. It is an elementary feed-back system, but since it is also represented as an open system, all these elements are interconnected in a complex way, so that a dynamic imbalance exists between them, with continuous oscillation of controlled variables and mutual regulations. Integration is either horizontal, between cells or between organs, or vertical, between molecular and cell systems, cell systems and organs, or organs and the body as a whole. Our model is therefore not a reductionist or mechanistic view of homeostasis but open to many implications typical of far-from-equilibrium dynamic systems, i.e.

—sensitivity to minor changes in variables and amplification of small signals
—chaotic behaviour, bistability and fractal structures
—spatio-temporal oscillation of homeostatic variables
—marked dependence on context (living systems as open systems or dissipative structures)
—occurrence of inverse effects of the same signal when applied in different conditions
—self-organization.

The possible contribution of chaos theory to the understanding of low-dose and ultra-low dose effects has been discussed elsewhere.[1, 18, 19]

Stressful stimuli

Let us now consider (Figure 3B) how this model system is modified when pathological changes come into play, shifting the equilibrium of a given variable *A/A'* excessively towards *A'*. Variable *A* may thus be regarded as the normal and *A'* as the pathological condition, in the sense of excessive oscillation of the parameter under consideration. Another possibility is that *A'* is a pathological event such as a foreign antigen or a toxic molecule; the subsequent chain of events does not change. At this point *A'* produces an enhanced signal *a'* which results in powerful activation of the regulatory system. In analogy with the concept of priming we postulate that, following an increase in signal *a'*, the specific receptor system is primed by exposing a greater number of receptors for *a'* (see the homologous priming phenomenon mentioned above).

The primed regulatory system increases its activity by producing more of signal *r*, which in turn will force the effector mechanisms (*A'*→*A*) towards the normal condition *A*. In this initial phase of the disease, the body reacts logically and efficiently in the direction of equilibrium and healing. Thus if *a'* is a molecule 'judged' to be abnormal in quality or quantity by the immunoregulatory system, the system will produce more receptors for *a'* (in this example, cytokine receptors and antigen receptors) and more *r* signals (antibodies, cytokines, interferons) which in turn prompt the effector system (phagocytes or complement) to restore normal homeostasis by eliminating the excess of *A'* and re-establishing the condition *A* (healing).

Other phenomena worthy of note occur in this initial stage of the disorder, which may be regarded as perfectly 'physiological'. The first of these is the onset of symptoms. Symptoms are usually linked to the activation of endogenous systems, more than to a direct effect of the aetiological agent. The symptoms thus stem from the effects produced by *a'*, activating the specific homeostatic systems, by *r*, produced by the regulatory system, and by other systems networked with the systems under consideration. Symptoms are the expression of the oscillation of given variables (in this case the variables can be seen as the number of signal molecules) beyond normal threshold limits. For example, fever, tachycardia, loss of appetite, anxiety, muscular weakness and pallor are all symptoms deriving from the reaction of phagocyte and autonomic systems (increased production of several cytokines, stimulation of hypothalamus-hypophysis-endocrine system axis, sympathetic and cardiovascular systems activation, and so on) to the stress caused by microorganisms penetrating into connective tissues or blood. The differences in the expression of these symptoms in different individuals reflect their particular endogenous (genetic or acquired) reactivity to a given harmful condition.

With reference to classic homoeopathic theory, as outlined in § 63 of the *Organon*, it may be said that the effects of signal *a'* correspond to the 'primary action', those of signal *r* to what Hahnemann called the 'secondary action' of the medicine, which is believed to be of a 'life-preserving nature'.

A second event worthy of note, illustrated in Figure 3B, is development of sensitivity to exposure to new receptors by the regulatory

system involving substances or signals other than *a'*. This event, too, belongs to the category of 'priming' events (heterologous priming) and, in general, to all modifications of receptor sensitivity and homeostatic system compensatory activity that relate to pathological conditions. The homeostatic systems involved in reactive regulation are thus altered not only specifically by the aetiological agent, but also on a broader spectrum. In other words a stressed system shows long-lasting or permanent modifications. We may call this primed state sensitization, or memory, or immunity, or conditioning depending on the kind of physiological phenomena involved.

Suboptimal recovery and chronicization

After the initial reactive phase, if interference with homeostasis continues, the regulatory system may undergo a major change in status. It adapts to the changed conditions, progressively suppressing its sensitivity to the persistent, abnormally increased signal (Figure 4A). This adaptation enables the system somehow to 'survive' with the disease which otherwise would require excessive expenditure of energy (continual activation of both the $A \rightarrow A'$ and $A' \rightarrow A$ mechanisms). From the molecular point of view, the cells reduce the receptors for *a'* to the point where they disappear altogether, or they reduce their affinity, or decrease communication with the effector systems (in our case, production of *r*). By and large, this phenomenon is specific at receptor level. That is to say, *occupied* receptors disappear, whereas the others remain or even increase in number. In other words, desensitization tends to be agonist-specific (though obviously exceptions and variants are possible in terms of combination of groups of different receptors, overall exhaustion of all cellular activities, etc.).

This is the second phase of the homeostatic reaction to a stressful stimulus. It may be considered to be the biological representative of chronicization. The homeostatic imbalance (the true disease) is now self-maintaining due to the suboptimal response by one or more homeostatic systems.

The important thing to note is that perpetuation of the disorder may continue even if the starting agent is no longer present. This may be because the network of many interrelated homeostatic systems can be set in several different schemes of behaviour (patterns) that correspond, roughly

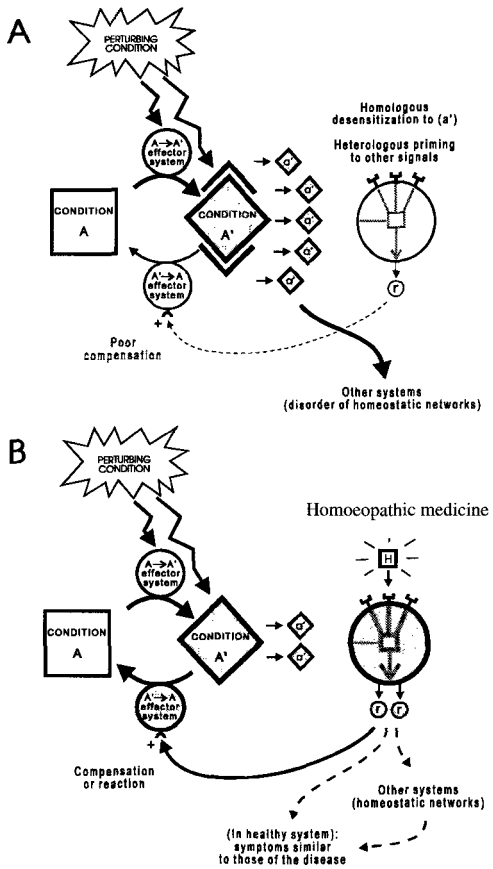

FIGURE 4. A) Disorder in a homeostatic system due to persistent interference. B) Schematic and highly simplified representation of the possible way by which a drug with a "homoeopathic" mode of action (*H*) may reactivate the regulatory system and the homeostasis.

speaking, to different 'attractors' or attractor basins. The system can be set in an attractor, can 'learn' and consolidate this 'pathological behaviour' and thus be unable to find the right way to change back to healthy behaviour.

It is evident from Figures 3B and 4A that regulatory systems 'recruited' by increased signals, i.e. regulatory systems involved in the disease, exhibit new and marked sensitivity to other signals. Below, we will show how the new sensitivities triggered by the disease process may serve to detect the modalities by which the disease is expressed (i.e. the significant signs and symptoms). This is very

important in homoeopathic procedure, because the indicated medicines should be found by applying the similia principle.

Homoeopathic regulation

Having reviewed the major dynamic events occurring in the model of a typical disease, the question arises of how to stimulate the recovery of homeostatic communication that has been blocked or diverted. According to our model, the regulatory system should be stimulated through primed sensitivities, not the receptors for *a'* (primary) signal. We should therefore by-pass homologous desensitization and utilize other sensitivities of the same system to push the homeostatic balance in the right direction. This applies not only to homoeopathy, but is the rational approach followed in mainstream scientific modern medicine.

Modern pharmacology has discovered a wide range of molecules acting on homeostatic systems. Modern treatments founded on this principle, using low doses of biological compounds to stimulate the recovery of the homeostatic system include cytokine therapy in immunocompromised patients, use of endotoxins as immunostimulants, treatment of immune disorders with immunoglobulins, use of nitric oxide in respiratory diseases, the administration of oral myelin in multiple sclerosis or oral collagen in rheumatoid arthritis, use of bacterial extracts in recurrent bronchitis and oral allergens in allergic diseases and therapeutic vaccination to cure cancer. We may also refer to the use of soluble receptors and in general to the new branch of pharmacology called peptidomimetics.

A number of animal models are based on this principle. One of them was developed by Dr Anita Conforti in Verona in collaboration with us,[20] showing that injection of low doses of immune adjuvant (based on killed *Mycobacterium butyricum*) into the rat peritoneum can prevent and cure arthritis induced by injecting high doses of the same adjuvant into the paw.

Most of these treatments are still in the experimental stage. The principle of stimulation of endogenous healing mechanisms on which they are based is known, but the physiological and biochemical details by which they act are far from clear. One often reads that the treatments work but nobody knows why.

The main problem is however the following. Does the physician know the primed receptors and their specific signal molecules in every individual case of disease?

As a matter of fact, when loss of homeostasis is due to multiple factors and subtle causes it is often hard to identify the biochemical blocks and the specific molecules to be supplied. Modern medicine has accumulated a lot of knowledge about the molecular basis of diseases but it is often not possible to understand the dynamics of complex homeostatic systems exactly. This is particularly true when dealing with personality profiles and subtle functional disorders, but we know that these have great impact on the health of individuals. How can we regulate them? We suggest that in these cases the application of the similia principle may be appropriate for the following reasons.

Referring to our basic model, necessarily highly simplified, we are in a position to postulate the mode of action of the homoeopathic medicine (Figure 4B). This activates the regulatory system via receptors other than those for *a'* which however produce the same effect, namely that of restoring production of signal *r*, activating the compensatory mechanism $A' \rightarrow A$. The homoeopathic drug is therefore thought to act in lieu of *a'*, to which the system is no longer sensitive as a result of adaptation.

The homoeopathic drug is thus postulated to interact with the regulatory system(s) concerned in the pathological change in homeostasis, having been identified precisely for its ability to cause symptoms similar to the disease, i.e. symptoms similar to those caused by mediator *a'* activating the regulatory system. It is clear that, since most of the symptoms in a pathological condition are due to activation of homeostatic reaction systems, it should be possible somehow to 'reproduce' the activation of the same homeostatic systems by administering a compound which 'reproduces' the symptoms of the disease in a healthy and sensitive subject. Theoretically, symptoms similar to those of the disease may be produced by administering *a'* and *r* or a substance or signal that activates the regulatory system via receptors other than those for *a'*.

Signal *a'* is already present in large amounts in the diseased system, but if the mechanism of receptor adaptation comes into play, the regulatory systems may become 'paralysed', inefficient and unbalanced. Since,

however, the regulatory system preserves other sensitivities in the disease state, and probably accentuates them (see the priming phenomenon), if other sensitivities are brought into play through other signals, the system can be reactivated. Subjecting the regulatory system to a signal 'similar' to *a'* (in the sense that it causes similar symptoms), the response *r* is elicited and thus a return to normal homeostasis. Similarity thus exists between the symptoms caused by activation of reactive mechanisms by the disease process in the patient on one hand and the symptoms caused by activation of the same reactive mechanisms in a healthy subject by a biologically significant external agent (in this case, the homoeopathic drug) on the other.

Having tried several drugs on healthy systems and identified a specific drug that causes that typical pattern of symptoms ('provings'), we can assume by hypothesis that in a person affected by a natural disease (lack of homeostatic communication) that specific drug will help the homeostatic systems to restore homeostasis by introducing the correct information. The medicine will subtly stimulate the regulatory systems using receptor sensitivities different from those blocked by the disease and this is exactly what the whole system needs to recover from the disease. If the initial stressor is no longer present, the network will eventually find a way of re-entering the previous attractor and thus become healthy.

Conclusion

Summing up, the hypothesis put forward is based essentially on the following points:

—In the dynamic progression of a disease process, specific homeostatic regulatory systems may break down or be blocked following excessive stimulation or interference from other pathological factors (metabolic and nutritional problems, toxic factors, heterologous desensitization, neurohormonal disorders, water-electrolyte imbalance or simply as a side effect of high-dose drug therapy).

—For as long as the disease process does not lead to profound and irreversible damage to regulation systems, the blockage can be by-passed using different receptor sensitivities (for exogenous or endogenous signals) which the disturbed systems preserve or even accentuate.

—The identification of suitable substances (or signals) for reactivating homeostatic systems specifically blocked in a given disease process is difficult to achieve with precision in any single patient using the conventional scientific approach, because of the complexity, variety and multiplicity of the systems involved and the dynamic and changeable nature of diseases.

—The homoeopathic approach, particularly by use of analogy (law of similars) makes it possible to get closer to identifying specific compounds (or signals) capable of interacting specifically with the homeostatic systems involved in the disease process in each individual case.

This is the genius of Hahnemann's homoeopathy, but it should not be seen in theoretical conflict with modern, scientifically-oriented molecular medicine. Both approaches use analogy, although with different standpoints. With mainstream pharmacology the aim is to regulate by means of a molecular analogue identified as the right molecule for the right receptor or for the right target system (if known). With homoeopathy the aim is regulation using a 'functional analogue'. We call this kind of analogue functional because it is characterized by the function that it exerts on the target system, causing symptoms to appear in healthy subjects and restoring homeostasis in sick subjects. According to the similia principle, careful analysis of functional analogy between the medicine and the patient's symptoms can be used to identify the correct prescription even in the absence of detailed knowledge of specific molecular/receptor interactions between homeostatic networks. On the other hand, the investigation and the identification of some molecular mechanisms involved in the action of homoeopathic remedies is not theoretically impossible and this is the field where modern scientific research and homoeopathic empirical observations may meet and overlap.

Mainstream pharmacology may appear to be more scientifically 'precise' when the exact mechanism of the disease is known and specific medicines can be administered. However, such precise action of conventional drugs is well known to be frequently associated with unavoidable side-effects due to interaction of high doses of chemicals with

complex homeostatic systems at various levels. Homeostatic networks at various levels may be profoundly affected by drugs that may act either as powerful stressors or factors 'blocking' the delicate, dynamic biological equilibria. Our general model therefore predicts that the homoeopathic approach—based on the use of low doses of carefully selected drugs to stimulate homeostasis at multiple levels—may be more effective when the complex, subtle and individual dynamics of the disease are considered. The homoeopathic approach, based on identification of functional analogy, may have a number of advantages:

—Symptoms are the expression of the typical reaction of individual homeostatic systems.
—The appearance of symptoms is very sensitive and often the earliest sign of a homeostatic disorder.
—The language of symptoms is psycho-somatic and complex by nature; it may also be interpreted as a symbolic language of the body.
—Use of low doses or high dilutions should avoid problems of toxicity and accumulation of chemicals in tissues.
—Symptom analysis is cheap, since it does not require high-tech instrumentation.

Taken together, these considerations lead to the suggestion that homoeopathy is a rational exploitation of homeostasis in complex systems. Clinical application of the similia principle may of course also present potential risks that have to be taken into account, the most important of which is to let severe diseases that begin with subtle functional symptoms go undiagnosed. As we are dealing with the complexity of the human being, it is very important to consider the application of this method to each individual patient as an experimental and hypothetical approach. If this *caveat* is taken into consideration, homoeopathy could be a possible option for the modern physician and a guide at the ultra-complex level, dealing with the intimate nature of diseases (their 'essential internal nature', as Hahnemann called it in the 1st paragraph of the *Organon*). Well-conducted clinical studies will be needed to confirm this hypothesis.

We have not considered the question of homoeopathic dilution and dynamization in our models. We suggest however that the proposed explanation of the mechanism of the similarity principle does not change in its essential meaning if the medicinal action is seen as an effect of direct molecular interaction or of biophysical electromagnetic interactions based on the permanence of structural or electrodynamic cohesion in aqueous solutions, as accumulating evidence suggests.[1, 21–24] It has been reported that important biochemical processes, such as cAMP-dependent protein kinase,[25] intracellular Ca^{++} [26] and heat-shock proteins[27] are regulated by low-frequency electromagnetic fields and that aqueous solutions treated with millimetre electromagnetic waves acquire and maintain the capacity to influence Ca^{++}-dependent K^+ channel function.[28] Assuming information storage in water to have a physical basis and both biochemical and bioelectrical homeostasis to exist in the body,[29] it is possible to speculate that relevant signal transduction mechanisms like those described are the target also of high-potency homoeopathic medicines. Further studies will be needed to clarify this critical point of homoeopathic theory.

Scientific and rational understanding of the similarity principle—undoubtedly one of the most interesting lines of thought in the history of medicine[30]—provides a basis for new experimental projects aimed to clarify apparently paradoxical findings and a more fruitful dialogue between different medical approaches in the one and only field of medicine.

Acknowledgements

We thank the companies Guna (Milan), Heel (Baden-Baden), Boiron (Lyon, Milan) for their support in various experimental studies and Kent Homeopathic/IDEAnet for providing homoeopathic software.

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