

## Lecture Series

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# Immunology and Homeopathy. 5. The Rationale of the ‘*Simile*’

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The foundation of homeopathic medicine is the ‘Similia Principle’, also known as the ‘Principle of Similarity’ or also as the ‘Simile’, which reflects the inversion of pharmacological effects in healthy subjects as compared with sick ones. This article describes the inversion of effects, a widespread medical phenomenon, through three possible mechanisms: non-linearity of dose–response relationship, different initial pathophysiological states of the organism, and pharmacodynamics of body response to the medicine. Based on the systemic networks which play an important role in response to stress, a unitary and general model is designed: homeopathic medicines could interact with sensitive (primed) regulation systems through complex information, which simulate the disorders of natural disease. Reorganization of regulation systems, through a coherent response to the medicine, could pave the way to the healing of the cellular, tissue and neuro-immuno-endocrine homeodynamics. Preliminary evidence is suggesting that even ultra-low doses and high-dilutions of drugs may incorporate structural or frequency information and interact with chaotic dynamics and physical-electromagnetic levels of regulation. From the clinical standpoint, the ‘simile’ can be regarded as a heuristic principle, according to which the detailed knowledge of pathogenic effects of drugs, associated with careful analysis of signs and symptoms of the ill subject, could assist in identifying homeopathic remedies with high grade of specificity for the individual case.

**Keywords:** action–reaction principle–biologic networks–homeopathic medicine–hormesis–inverse effects–paradoxical pharmacology–response to stress–self-organization–Similia principle–Wilder’s rule

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## Introduction

The cardinal principle on which the theory of homeopathic medicine is based is that of ‘similarity’, according to which a homeopathic remedy in a healthy subject will produce certain sets of symptoms, while the same remedy will cure similar sets of symptoms in unhealthy (sick) subjects (1–3). Hahnemann’s theory withstands the test of time, and has been supported by scientific findings

in an array of fields, including that of immuno-allergology, as described in previous lectures on the subject (4–7). This principle can now be integrated into a broad theory of the homeodynamics of living systems (Table 1).

Indeed, there is a need for viable hypotheses of homeopathy mechanism of action. One of the earliest systematic reviews of homeopathic clinical trials concludes: ‘... *The amount of positive evidence even among the best studies came as a surprise to us. Based on this evidence we would readily accept that homeopathy can be efficacious, if only the mechanism of action were more plausible*’ (8).

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**Table 1.** The homeopathic simile and regulation of body homeodynamics

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|-----|---|
| (a) | Homeopathy is a therapeutic method based on the application of the similia principle, utilizing medicinal substances that, in healthy subjects, produce effects that are similar to the symptoms being treated in ill subjects.   |
| (b) | When a healthy organism is perturbed by every physical, chemical, or biological stressor, it produces characteristic signs and symptoms; when caused by a drug, this is regarded as an expression of iatrogenic response or pathophysiological reaction ('proving' in the homeopathic medical system).  |
| (c) | The provings that describe the characteristic patterns of signs and symptoms, caused in healthy subjects by a number of mineral, vegetable and animal compounds, have been gathered during the past two centuries in the homeopathic 'Materia Medica'.  |
| (d) | When threatened by natural disorder or disease, living organisms show signs and symptoms which are mainly the expression of the efforts to re-establish normal homeodynamics at cellular, tissue and systemic levels including the mind. In chronic conditions, the symptoms also reflect the failure of those efforts, the blockade of regulation system(s), and the pathological adaptation to the disease. |
| (e) | Low doses or high dilutions of a substance which is capable of evoking certain symptoms in healthy subjects, when administered to subjects showing similar symptoms due to natural diseases, may evoke a specific and global secondary healing reaction, thus becoming a potentially effective therapeutic agent.   |
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Another controversial principle of homeopathy is that the strength of a remedy would be increased through its dilution, which is a process known as *dynamization*, or *potentization*. At the end of this report, we will briefly discuss this issue. In any event, there is the need to clarify a preliminary assumption: both molecular and non-molecular information (i.e. mechanic, acoustic, electromagnetic, quantum electrodynamic) operate biologically, and regulation through the 'simile' could work in both cases, since they are not conflicting one with the other.

The purpose of this lecture is to re-evaluate the principle of similarity through up-to-date scientific knowledge concerning many phenomena, from cell behavior to clinical practice (9–11). This will allow us to extrapolate a general working hypothesis according to which biologically active compounds (including highly diluted solutions) could have inverse or paradoxical effects, based on one or a combination of the following factors:

- (a) non-linearity of response to different doses of the compound/signal,
- (b) pathophysiological state of the treated organism and
- (c) pharmacodynamics of the drug, particularly with regard to the rebound effects and long-term adaptation.

### Non-linearity of the Dose–Response

In biological systems, non-linearity between dose and effect is the rule, rather than the exception. Even if this phenomenon does not clarify all the clinical effectiveness of homeopathy, the following controlled experimental models examine the similia principle.

#### Hormoligosis

The terms 'hormoligosis' and 'hormesis' refer to stimulation of biological systems by low-dose toxins and inhibitors, as shown in a number of experimental models (12–20). Early attempts to describe hormesis

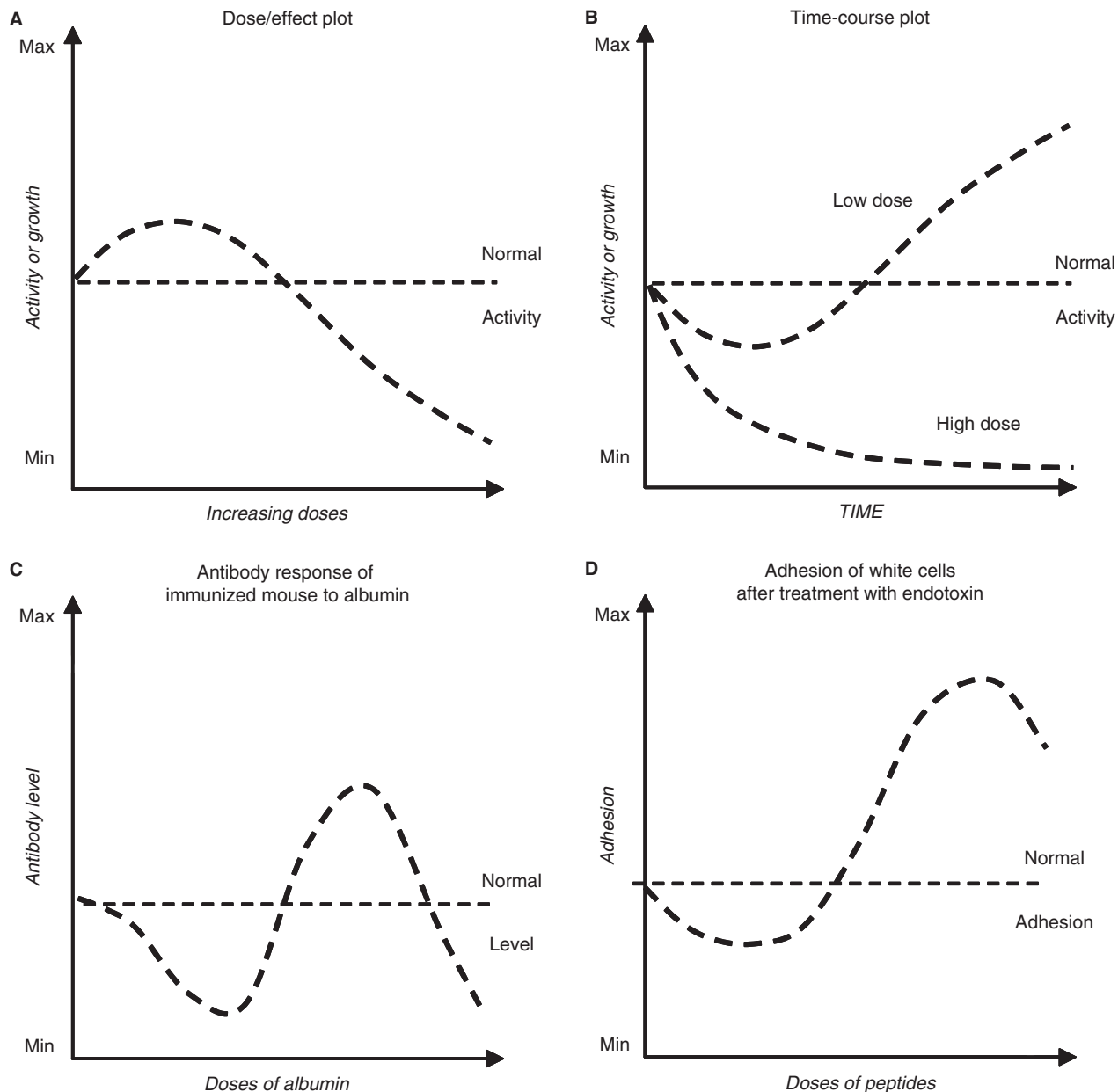
date back to 1877 when Schulz, while studying yeast metabolism, proved that almost all poisons have a weak stimulus effect at low doses (21,22). Together with R. Arndt, he then developed a principle, the so-called 'Arndt-Schulz law': '*weak stimuli slightly increase biological responses, medium–strong stimuli markedly raise them, strong ones suppress them and very strong ones arrest them*' (23).

In general, these hormetic effects can be documented by reverse-U dose–response plots or even more complex dose–response curves. In Fig. 1A, a typical hormetic (reverse-U shaped) curve is shown. Figure 1B shows the kinetic of low-dose and high-dose effects of inhibitors on a biological system: an overcompensatory response follows the initial decrease in activity due to inhibitor low doses. This may optimize the ability of an organism to meet challenges beyond the limits of normal (unexercised) adaptation.

#### Inhibition by Low Doses

A wide variety of substances exert opposing effects (inhibitory or stimulating) at low or high doses; this phenomenon is well documented in immunology. Figure 1C shows how specific antibody levels can change in mice inoculated with different antigen (bovine serum albumin) doses. At low or high antigen doses, the murine immune response is depressed (immune-tolerance), while there is a positive antibody-production response at intermediate doses.

Various factors contribute to the result, in conjunction with specific lymphocyte subset activation, different receptor sensitivities and the role of the tissue environment on the cell activation/suppression. At least two different mechanisms are responsible for T-cell auto-reactivity: high concentration of self-antigens causes cell depletion, while low doses cause a specific inhibition, known as bystander suppression. This low-dose regulation could be used to explain the effects of some homeopathic medicines (24). However, even with much scientific evidence, the concept of hormetic dose–response relationship is not integrated by mainstream schools of thought in toxicology (25).



**Figure 1.** Examples of biphasic or polyphasic dose–response curves.

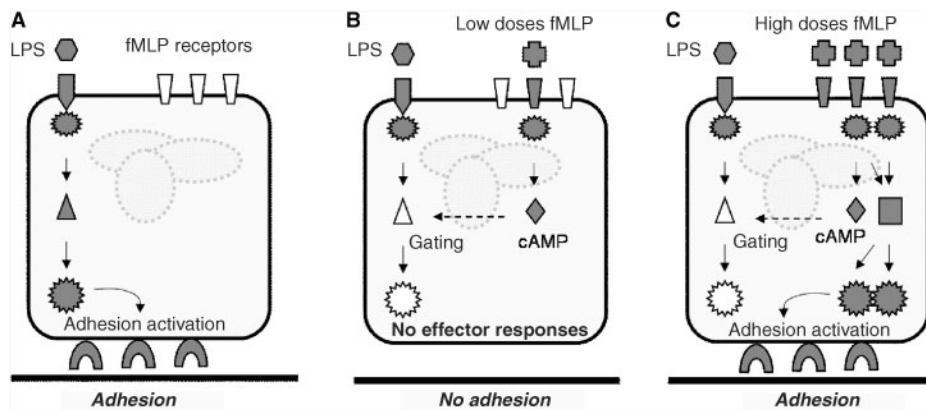
### Inverse Effects in a Leukocyte Model

The activation of human neutrophils shows a dose-dependence on bacterial peptides (Fig. 1D) (26,27). High doses ( $10^{-6}$ – $10^{-7}$  M) of bacterial peptides formyl-Methionyl–Leucyl–Phenylalanine (fMLP) were able to induce a marked increase in adhesiveness of human leukocytes, whereas 100 times lower doses ( $10^{-8}$ – $10^{-9}$  M) inhibited and reversed the adhesion induced by bacterial endotoxin (LPS) (28) or by migration into the inflammatory exudate (29).

This paradoxical effect of low-dose fMLP models is probably due to the ‘gating’ exerted by cyclicAMP (cAMP) at the level of intracellular signal transduction

pathways (26). Figure 2 shows a schematic representation of a LPS-treated cell, with no fMLP (A), and low (B) and high (C) doses of fMLP. The latter bacterial peptide at low doses does not stimulate adhesion, whereas the intracellular cAMP increases, through activation of adenylate cyclase. cAMP is an intracellular messenger for many enzymes, including protein kinase A which, in turn, can inhibit the LPS-activated transduction machinery of adhesion (gating pathway). fMLP at high doses obtains full activation, using a different transduction pathway (represented in Fig. 2 by squares), thus by-passing the gating by cAMP.

The importance of cAMP has also been invoked in explaining other phenomena which recall the



**Figure 2.** Schematic representation of the inverse effects of different doses of fMLP on LPS-treated human neutrophils.

‘simile’: interleukin-2 has opposite effects on B lymphocytes depending on intracellular cAMP levels (30); the inhibition of basophil responses by low doses (31) or high dilutions (32) of natural compounds may have a similar explanation at the level of signal transduction.

Furthermore, not only the gating theory explains the occurrence of inverse effects at a cell level: the presence of various receptors with both different affinities and different coupling capabilities to effector systems, or the induction of detoxification enzymes (gene expression and enzyme activation) should also be considered (33). Other authors (34–39) have elaborated different theories, based on the heat-shock protein system activation, or on the metabolism regulation and on toxicology. Those theories do not conflict with each other, but concern different levels of cell organization.

### The Role of Pathophysiological State

The role of inflammatory processes is to control the structural integrity of organs and tissues, while the immune system controls the specific identity, or biological ‘selfness’, of molecules within the organism. Those systems are integrated with the peripheral and central nervous systems (40): mood and behavior disorders are associated with immunopathological disorders, with susceptibility to recurring infection, hypersensitivity, allergies, autoimmune diseases and diabetes. Homeopathic therapy should act by regulating the inflammatory and immune systems, both directly through molecular similarity, as seen in isopathic therapies, and indirectly through systemic interconnections, as shown in Fig. 3.

### The Response To Stress

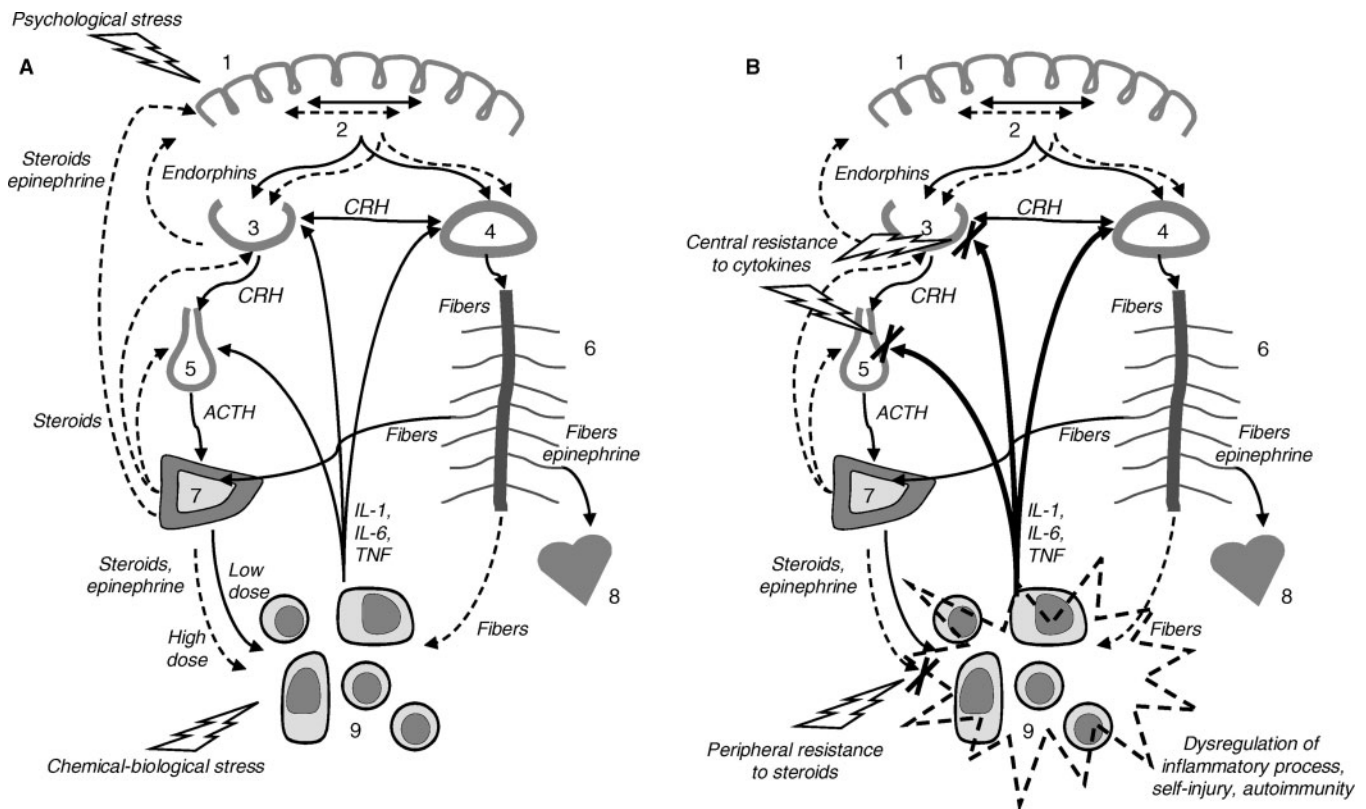
Figure 3A shows a typical sequence of physiological mechanisms which maintain homeodynamics in the immune and endocrine systems. Psychosocial stressors activate the neuroendocrine pathways which, eventually,

can lead to higher corticosteroid levels; uninterrupted strong stimulation can suppress the immune system, thus increasing susceptibility to infection (41,42). On the other hand, peripheral inflammatory cells are recruited and activated to counteract chemical or biological stress, producing molecular messages (cytokines) toward the central nervous system to build up a neuroendocrine response to stress. Increased steroid production, in conjunction with adrenergic stimulation, is important in a wide variety of adaptive responses, including regulation of inflammatory processes.

Repeated biological or physiological stress can cause internal communication failures, leading to the adaptation to a pathological state, more specifically, to chronic disease. Figure 3B depicts a typical loss of sensitivity to cytokines or to steroids. A variety of diseases are based on the lack of adaptability to environmental change through system or sub-system derangement. Immuno-deficiency syndrome, atopic dermatitis, encephalomyelitis, coronary artery disease, chronic heart failure, anxiety and depression all exhibit an altered coordination or disruption of neuro-endocrine signaling. For example, glucocorticoid overproduction, combined with depression and chronic stress, cause destabilization in the glucocorticoid receptors to the feedback inhibition of the hypothalamus–pituitary–adrenal (HPA) axis and to an increase of inflammatory cytokines (43). Some chronic diseases, such as asthma, are considered as a type of pathologic adaptation of complex networks, which behave like semi-stable ‘attractors’ within the organism (11,44). This self-maintenance of disease, as organization of pathologic attractors in complex systems, can be regarded as an update to the ‘miasm’ concept of classic homeopathy (11,45–47).

The above theoretical background suggests that homeopathic medicine can regulate inflammatory and immunopathological processes as well as the neuroendocrine network and peripheral receptors. Homeopathic information mimics a pathophysiological stress, because it is able to induce symptoms of pathology, and, in



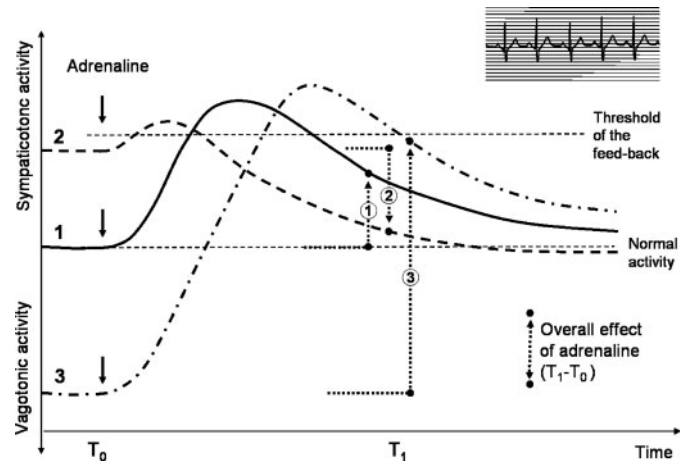


**Figure 3.** Typical neuroimmunoendocrine networks involved in the response to any type of stress (A) and possible dysfunction in chronic inflammatory diseases (B). 1. Cognitive functions, 2. neural networks, 3. hypothalamus, 4. locus ceruleus, 5. hypophysis, 6. sympathetic nervous system (adrenergic), 7. adrenals, 8. cardiovascular system, 9. immune system and inflammatory processes. ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; IL-1, interleukin-1; IL-6, interleukin-6; TNF, tumor-necrosis factor; → stimulation, --→

the ‘already-stressed’ and inefficient organism, would re-activate a coherent response. In fact, homeopathy could have a positive effect on stress-induced behavior and on gastric and immunologic alterations in mice (48). Highly diluted histamine shows to be active on blood basophils, on skin inflammation reactions and on sleep patterns in rats (5,49).

**The ‘Initial Value’ Rule**

Biological responses strictly depend on the ‘starting conditions’ of any tissue or organ, and different starting conditions yield peculiar reverse responses to a drug. An example of different effects due to different cellular conditions can be found in macrophages—these cells are known to be activated, for example, by cytokines in a number of biological events including chronic inflammatory reactions, tumor defense, repair phenomena, atherosclerosis and so on. Interferons, endotoxins and tumor-necrosis factors (TNFs) increase resting macrophage functional capability, whereas they suppress previously activated macrophages (50). A related phenomenon was described by Wilder in the first decades of the past century in experimental settings (2,51,52). A typical report of Wilder’s findings is shown in Fig. 4.



**Figure 4.** Diagram of the effects of adrenaline (epinephrine) on the cardiovascular system (the ‘initial value’ rule of Wilder). For explanation, see text.

He recorded heart frequency and blood pressure (not shown in the figure) in dogs before and after the administration of 1 mg adrenalin.

Under normal conditions (Fig. 4, line 1) the drug causes an increase in both heart rate and blood pressure; these then plateau and finally revert to the resting state.

This kinetic is due to the activation threshold of homeodynamic feedback response, conceivably due to vagus stimulation and to the inactivation of the stimulant. However, when the initial heart rate is elevated (high sympathetic tone of the test animal), the exogenous adrenaline response is different—the initial increase is less, prior to returning to the resting state (line 2). Thus, the net effect of the drug is the decrease in heart rate when compared with the initial rate. Starting with very low heart rate (vagotonic state, line 3), the response to adrenaline is higher than in normal animals, due to the system's higher sensitivity to the drug and to a slower homeodynamic feedback threshold.

In humans, bronchial asthma is characterized by the increase of vagus activity on smooth bronchial musculature; under these conditions, adrenaline supports breathing, thanks to its dilating and relaxing effects. On the other hand, in normal subjects, adrenalin has little or no effects. In conclusion, the same treatment or similar treatments can cause different, if not opposite, effects, depending on the initial state of the system. This typical behavior has been described in different physiological systems (cardiovascular, hormonal, respiratory, nervous, etc.) and using various drugs (53,54).

More recently, a preliminary mathematical model of the action–reaction principles was developed looking at the ‘weak quantum theory’ and the ‘patient–practitioner entanglement’, based on the metaphor of a hypothetical gyroscope as physical representation of the vital force (55). Briefly, increase or decrease in the rate of spin of a hypothetical gyroscope (namely the ‘vital force’) was described in terms of quantized ‘shift operators’ constructed mathematically from the ‘complementarity’ of a remedy's primary and secondary symptoms. Therefore, the vital force was studied as a ‘wave function’ able to illustrate the biphasal action of remedies encapsulated in the Arndt–Schulz law, Wilder's law of initial value and some of the results of homeopathic provings.

### Rebound Effects and Paradoxical Pharmacology

Inverse drug effects are evident by changing their schedule or treatment duration, or the observation period of the therapy: short treatment can be stimulating, whereas longer treatment can be inhibitory (or opposite, based on the experimental model). This area includes the so-called ‘paradoxical pharmacology’ (56): chronic and acute treatments produce opposite effects, similar to those of a single physical exercise, which will increase blood pressure, whereas ongoing training will regulate it. Obvious evidence of these phenomena is observed in receptor-mediated events and in heart failure progression: the time-course of  $\beta$ -blocker treatment during heart failure can be described as an immediate worsening of

the patient, whose condition then improves, with a net result of a decrease in death by heart failure in the long term. This paradox can be described in terms of beta-receptor protection from overexposure, which is a phenomenon generally associated with desensitization and decreased signaling.

In addition to analgesia, opioids cause hyperalgesic effects, depending on whether treatment is acute or chronic, which have many clinical implications (57). Antiepileptic drugs can frequently aggravate epilepsy by way of an inverse pharmacodynamic effect (58). The same secondary reaction of the organism can be described for hundreds of modern drugs, including antiinflammatory agents (59), and can be referred to as the rebound effect. The drug's primary effect forces the organism toward a reaction against its own upsets by way of a vital (paradoxical, secondary or compensating) reaction.

If acute and chronic responses are often opposite in nature, and if the drug's counter-indications are based on its acute effects, it is possible to find scientific input to study paradoxical pharmacology—the list of drug contra-indications, since ‘*the opposite of contraindicated is indicated...*’ (56). A rapid initial decline may produce long-term beneficial effects (60,61). Therefore, paradoxical and rebound effects could be considered curative, thus allowing a connection between homeopathic ‘*simile*’ and traditional pharmacology (62).

### General Model of the ‘*Simile*’

Having analyzed a few possible applications of the ‘similarity’ in biological systems, we will now describe a general model of this core principle of homeopathy. In previous studies (10,11,27,63), the concept of ‘*regulation of stressed homeodynamic networks*’ was introduced, based on how the networks react to stress, and on the possible role of homeopathic self-recovery regulation. Here we summarize and update this conceptual model, which can help rationalize the basic mechanisms of homeopathic simile on different levels of biological organization (molecular, cellular, organic and systemic).

### Homeodynamics of Biological Systems

The concept of homeostasis (more correctly referred to as ‘homeodynamics’), introduced by physiologist W. B. Cannon (64), refers to those activities which tend to maintain the variables of a vital system constant, or within acceptable limits. Hahnemann himself based his medical system on the action and reaction principle. In paragraph 3 of the ‘*Organon*’, he describes this fundamental principle: ‘*Every agent that acts upon 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 a 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, it is indeed an automatic action of our life-preserving power, which goes by the name of secondary action or counteraction'.

#### The Feed-back is the Core of Homeodynamics

To illustrate homeodynamic concepts, it is best to refer to the simple model in Fig. 5A. We will consider the variable A–A' in a state of imbalance and in reversible conditions due to the actions of two operator or effector mechanisms, which can move A towards A' and vice versa. We refer to A as the normal condition and A' as a far-from-equilibrium (stressed, or diseased) condition. No homeodynamic variable can properly function without a form of control, represented by one or more regulatory systems which receive information from A' in the form of signal 'a', which is associated with its specific state (for example, an enzyme reaction product proportional to how much of A' is present or to how much of A' is functioning). Having received the 'a' signals (for which it has specific receptors), the control system is activated and produces the 'r' signal, which inhibits the A–A' conversion, or activates the A'–A conversion. Figure 5A illustrates that the signals are considered capable of affecting other systems or other effector mechanisms, in the same way as the regulatory system can have different receptors which bind different active signals. Therefore, all homeodynamic systems are included in a broad network built on multiple elements. The model in this figure is simplified; in fact, it only shows the central feed-back structure of the complex biological homeodynamics.

#### The Reaction Phase

When a perturbing factor comes into play, the balance shifts to A' (Fig. 5B) and an increase of the 'a' signal occurs. The regulatory system, in turn, enhances its own activity, thus producing a higher quantity of the 'r' signal. For example, if 'a' is a signal molecule (e.g. interleukin-1, cytokines, interferons) released from inflammatory exudate, the immune system produces more 'r' signal (e.g. antibodies, interleukin-2), thus bringing the effector system (phagocytes or complement) back to its normal homeodynamic, by eliminating A' excess and re-establishing A condition (healing). In the initial phase of disease, the system reacts logically and efficiently in the direction of balance and health. Of course, if 'a' signal was an inhibitor, the A–A' perturbation would be followed by decrease of regulatory system's function (not described in the figure).

As shown in Fig. 5B, *symptoms* will appear when physiologic systems are under stress, far from the equilibrium. Symptoms are associated with endogenous regulatory system activation (or inhibition), more than

with the direct damage due to the stressor/pathogenic factor. In infectious diseases, for example, fever, fatigue, loss of appetite, tachycardia and skin rashes are the product of the organism's reaction, primarily due to molecular signals, such as complement factors, kinins, interleukin-6, adrenalin and TNF.

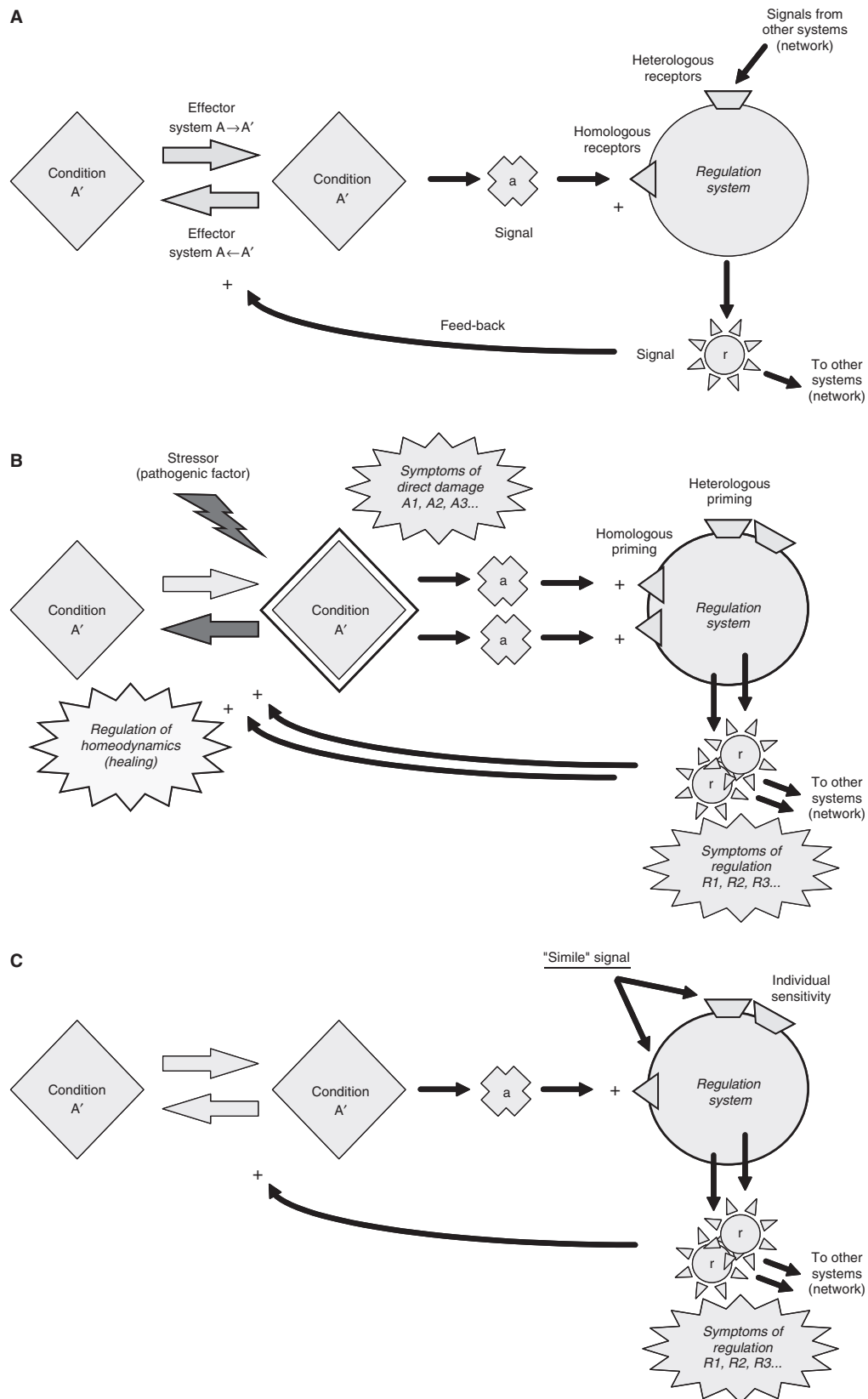
Generally speaking, the initial response of a regulatory system is associated with the *priming* of its own sensitivity with respect to the signal, represented in Fig. 5B as an increase in the number of surface receptors within the system. This pre-activation was described by us in leukocytes as '*homologous priming*' (65) and may also involve increase of receptor sensitivity or of signal transduction. However, priming is usually not specific, owing to the increase of sensitivity also to other stimuli (*heterologous priming*), here represented as the exposure of new receptors by the regulatory system for substances other than 'a'. This event is functional to adapting to new environmental conditions and to reinforcing network communications. For example, when a cell, such as a lymphocyte (a primary component of host defenses), becomes stimulated by a cytokine or another specific antigen, it becomes 'primed' to express a higher number of receptors to more compounds. Other examples of priming are bronchial reactivity in asthmatics following antigenic stimulation, liver induction of detoxifying enzymes following alcohol or drug ingestion, cardiac hypertrophy following physical exercise and increase of synaptic strength in neurons (memory).

#### Homeopathic Proving

Figure 5C shows a schematic view of homeopathic proving: in a 'healthy' regulating system network, an exogenous pharmacological signal could trigger many activities which mimic the reaction to stress. In accordance with homeopathic principles, because most symptoms derive from homeodynamic system activation, it should somehow be possible to reproduce their activation with a compound capable of provoking symptoms in healthy and sensitive subjects. Theoretically, *symptoms similar to natural reaction* can be reproduced by administering an activating (or inhibiting) substance through homologous or heterologous receptors. The resulting pattern of characteristic signs is the 'portrait' of a disease involving the same regulatory systems in reaction to a natural stressor.

#### Homeopathic Regulation

The traditional approach of mainstream medicine is essentially reductionistic and mechanistic—it is based on the identification and elimination of pathogenic factors (for example, antibiotic therapy), on the antagonism toward endogenous signals (such as anti-TNF antibodies) or on inhibition of hyperactive control systems (such as anti-inflammatory agents), or on their stimulation if



**Figure 5.** Schematic description of the feedback in biological systems (A), of normal homeodynamic reaction to stress and to pathogenic factors (B) and of the effect of 'simile' signal on healthy and sensitive systems (homeopathic 'proving') (C).



assuming they are inefficient (such as immunostimulatory agents) or, finally, on substitutive therapies (such as insulin for diabetics or bone marrow transplantation for severe immunodeficiency). This approach works in a number of circumstances, but when homeodynamic loss is due to many factors or to ambiguous causes, it becomes difficult to identify all the specific biochemical blocks or the specific molecules that would be required. For example, it is well documented that the psychological profile or subtle functional disorders negatively impact long-term health (40,66–68).

Taking into account its fundamental complexity, regulation can be obtained through the *similia* principle, starting with a new and holistic view of what constitutes the vital force and its possible dynamic alterations. To quote Hahnemann (Organon, para 29) ‘*every disease (not entirely surgical) consists only in a special, morbid, dynamic alteration of our vital energy*’. The ‘dynamic alteration of vital energy’ can be translated in today’s terms as both homeodynamic and communication disorders. By reference to our basic model we should distinguish two modes of action of the *simile*, the first one related to acute diseases, the second one to chronic diseases.

#### Acute Diseases

An acute disease (Fig. 6A) occurs when an external pathogen damages the organism, which in turn generates an excessive reaction, thus causing more damage—classic examples include rhinoconjunctivitis, abscess, thrombosis, panic attack, pneumonia, anaphylaxis, influenza and shock. Apart from any necessary attempt to eliminate or at least to reduce the pathogen, here the homeopathic intervention (Fig. 6B) could assist in decreasing the risk of excessive reaction.

This outcome could be obtained by using a remedy which, in healthy subjects, mimics the actual symptoms of the disease which are produced by the regulating system. In the diseased organism, which is already activated by the disease, the effect of ‘similar’ medicine is not an increase of symptoms, but, on the contrary, has the opposite effect as previously described (e.g.: non-linearity, hormesis, initial value rule). Consequently, the acute condition would continue its physiological course toward healing without the risk of excessive reactions and with fewer symptoms.

Other regulatory systems can become depressed in the course of acute disease (not shown in the figure), causing, for example, fatigue, anorexia, loss of concentration, etc. In such cases, the inversion of effects of the ‘simile’ drug would be associated with the stimulation of the affected regulatory systems.

#### Chronic Diseases

When the homeodynamic upset is continuous, following an initial reactive phase, the regulatory system may

undergo a significant change of status—it will adapt to its altered conditions and will progressively suppress its own sensitivity to the persistent and stronger signal (Fig. 7A). The adaptation thus enables the system to survive the disease in question, which would otherwise require an excessive expenditure of energy (continual activation of regulatory systems and of both the A–A’ and A’–A mechanisms). This phase can be considered the major factor of disease chronicization, as previously described in the HPA axis (Fig. 3B). The homeodynamic displacement is self-maintained by the suboptimal network response, through desensitization of one or more regulatory systems.

From a molecular point of view, cells can down-regulate specific receptors for ‘a’ to the point of complete elimination, or can reduce their affinity, or diminish signal transduction to the effector systems (in our case, the production of ‘r’). This phenomenon is quite specific on the receptor level—in other words, the occupied receptors disappear, while others either persist or at least increase quantitatively; desensitization tends to be agonist-specific. How different receptors behave in cells exposed to a change of functional state is clearly shown by our experiments comparing human neutrophils isolated either from blood or from skin inflammatory exudate of the same subjects (69). Inflammatory cells exhibited a respiratory burst in response to fMLP and to substance P that was 2- to 3-fold higher than the burst exhibited by blood cells (priming). On the contrary, the response to other stimulants such as concanavalin A was not primed and the response to TNF- $\alpha$  was decreased in exudate versus blood cells by about 50% (desensitization). Therefore, the inflammatory cells, compared with blood cells, appear to be at the same time primed, unmodified and desensitized, according to the different receptors involved.

Because the regulatory system conserves other sensitivities in the diseased state and, in all probability, also accentuates these sensitivities (see heterologous priming), the system can be reactivated. This is where we see the fundamental contribution of homeopathic tradition—in chronic disease (Fig. 7B), the homeopathic remedy, identified as the remedy which produces symptoms similar to those of the disease (considering its overall course, including ‘old’ symptoms and constitutional symptoms), would activate the regulatory system through receptors and sensitivities other than those for ‘a’, but which would produce the same outcome, by restoring the ‘r’ signal. This phenomenon would activate the counter-balance mechanism A’–A. The homeopathic drug is thus considered a functional substitute of ‘a’ to which the system is no longer sensitive because it has adapted.

The homeopathic remedy will stimulate homeodynamic feedback by latching onto perfectly efficient sensitivities that are not blocked by the disease. By recalling the medicinal effects on the healthy subjects (proving),

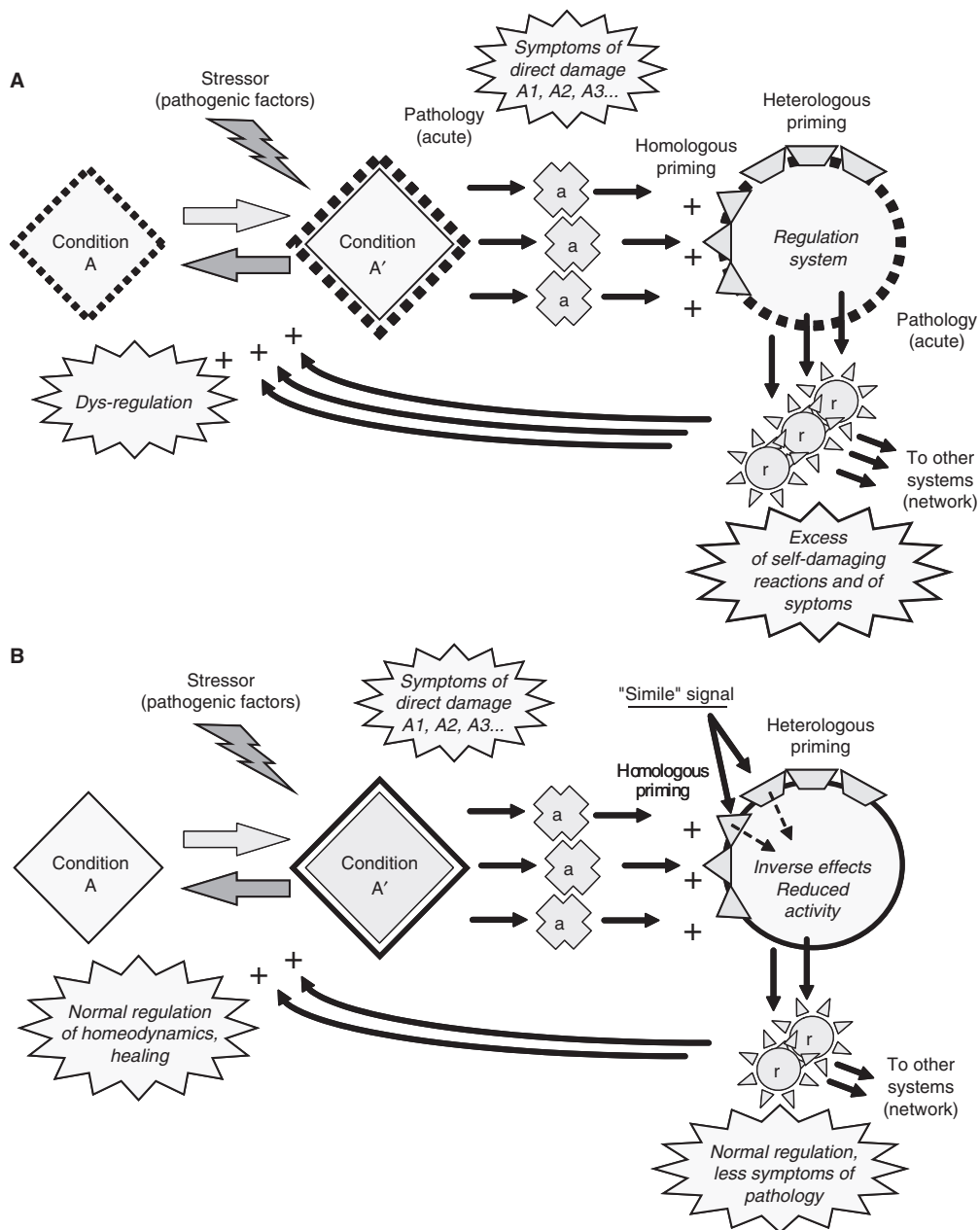


Figure 6. Schematic representation of the acute disease (A) and of the regulatory action of the homeopathic 'simile' (B).

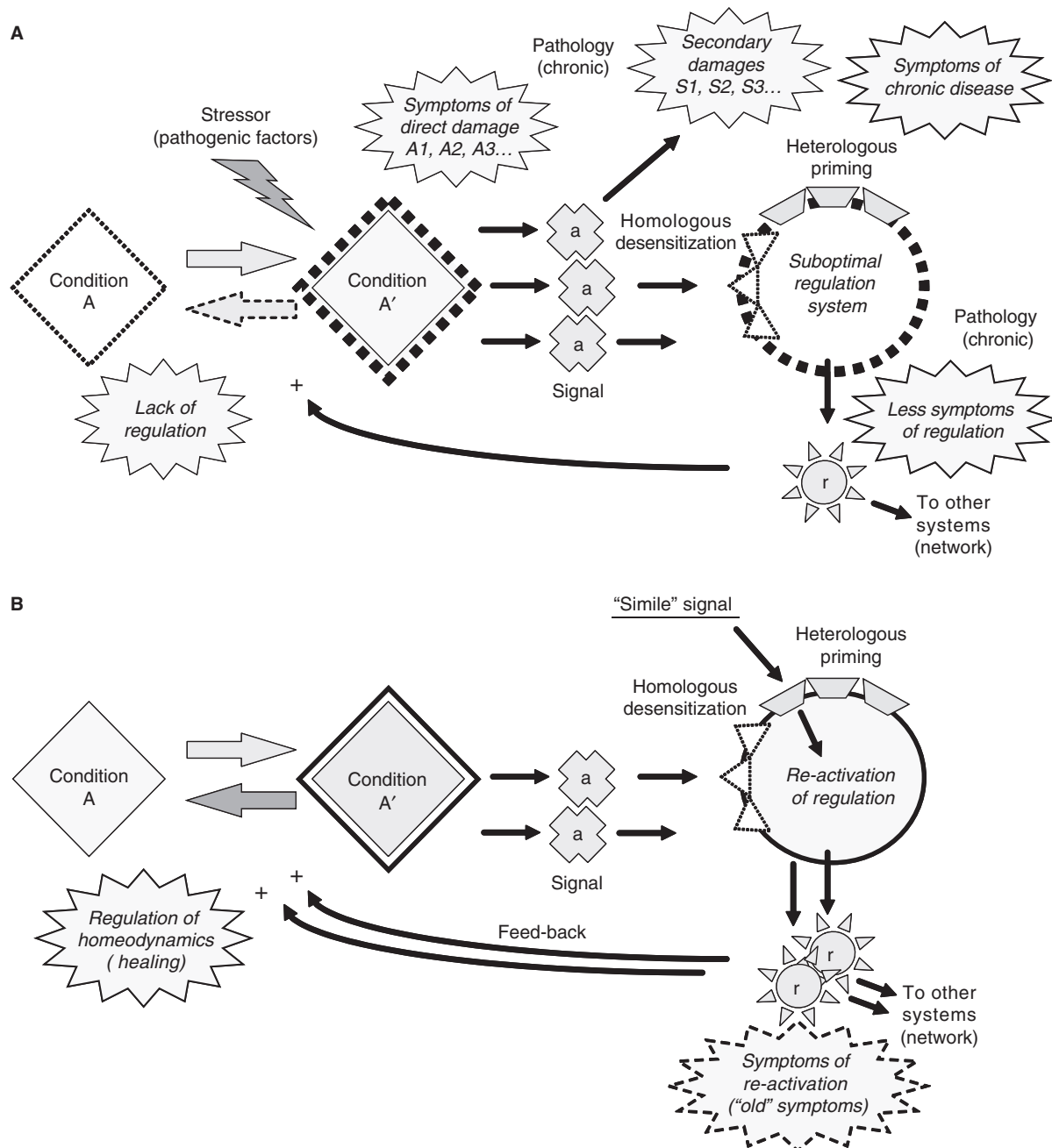
one can assume that in the diseased subject these medicines will assist in re-establishing the introduction of specific information. With the stress factor removed, the network will find its way (attractor) back to a healthy state.

### The Homeopathic 'Potencies'

The second major challenge of homeopathy is the use of ultra-low doses (more precisely termed high dilutions, or high potencies according to classic homeopathic parlance), i.e. those which contain virtually no molecules of the active compound. Even if the present study is

committed to the similia principle, a brief mention of the theories and evidence regarding how ultra-diluted homeopathic could act is warranted. Two basic questions need to be answered:

- Can a solvent, such as water or water-containing various percentages of ethanol, incorporate and maintain some information from the original solute?
- Admitting that some pharmacological information is endowed by homeopathic solutions, how could it be transmitted to the body and have therapeutic effects?



**Figure 7.** Schematic representation of the chronic disease (A) and of the regulatory action of the homeopathic 'simile' (B).

Briefly, most of the findings converge on a non-molecular (or 'meta-molecular') intelligence carried by solvent molecules (being water or a water/alcohol mixture), which could interact within the organism by way of resonance with biophysical regulatory systems (10,70–75).

### The Physical Nature of the Remedy

Many studies have been conducted to offer an in-depth explanation of the physiochemical nature of homeopathic drugs which have been highly diluted. A number of

experimental findings and physical theories support the possibility that water and ethanol molecules, which are typical solvents of homeopathic drugs, are somehow 'connected' in a type of dynamic, self-organizing networks, described as 'water clusters' (73,76–78). These physical states of the solvent could then encode the information necessary to activate the biological processes, possibly on the cell membrane level.

In the process of serial dilution and succussion, a homeopathic solution could undergo an increase of its physical structure, similar to geometrically grand and branched fractal images resulting from iterative

mathematical algorithm (10,79,80). Although today such a hypothesis is strictly speculative, recent scientific evidence directs us to study this elusive phenomenon. It is worth noting that laboratory models of homeopathic dilutions show alternating activity peaks (5,32). Homeopathic solutions, when compared with the control solvent samples, show increased electrical conductivity (81,82), distinct NMR signals (83), optical emissions (84) and characteristic thermo-luminescent patterns when undergoing electromagnetic impulses (85).

Furthermore, the concept of self-developing 'coherent domains' (CD) in liquid crystals and water, has been proposed to follow the quantum electrodynamic (QED) theories concerning condensed matter (86–89). The theory rests on the different behavior between the macroscopical assemblies of identical microscopical systems and classical microscopic interaction due to weak forces; the differences are exalted below the so-called critical temperature or above the 'critical' density. CDs are taking shape as the 'fundamental blocks' for condensed matter: atoms, molecules, electrons and nuclei tune inside blocks to a macroscopic (classical) electromagnetic field, thus allowing the efficient frequency exchange between different system's CDs. Some evidence suggests the effects of low-frequency electromagnetic fields on water (90) and on biological structures through changes in solvent structuring: microwave irradiated solutions modify the opening capability of cell membrane ionic channels even if irradiation stopped (91–93). The authors referred the phenomenon as 'electromagnetic memory of water'.

### Sensitivity, Complexity and Resonance

According to the dynamic systems theory, the whole organism and each cell can be described as complex systems where the 'equilibrium' is a special case of attractor, the integration of a number of attractors (94–99). As a consequence, healthy and pathological states become interpretable as different types of attractors, which may be converted from each other by bifurcations or critical perturbations. An important characteristic of those attractors are their chaotic dynamics, referred to as 'sensitive dependence on initial conditions and on perturbations'. Small differences of the starting conditions or perturbations of trajectories in the space-states produce important differences in the final phenomena (100–102).

Future studies on fractals and deterministic chaos will influence knowledge on physiology and pathology, enabling the characterization of the therapeutic effects of periodic stimuli (including physiological stress, acupuncture, electric pacing, psychotherapy and so on), different pharmacological compounds (103) and highly diluted homeopathic remedies (11,104–108). Very slight and highly specific signals could act at unison with the

resonant recipient system (s) thus becoming 'regulators' of its (their) dysregulation and unbalance, where the choice, at the bifurcation point, depends upon minor fluctuations between order and chaos.

In this connection, the possible effect of ultra-diluted and succussed medicines has a chance for a scientific explanation. The disease could be regarded both as functional or molecular-structural abnormality and as disturbance of the overall network of electromagnetic communications: long-range interactions act between oscillating elements (molecules, nerve centers, organs, to mention but a few), whose frequencies are coherent and specific, in other words, resonant. Therefore, disease is the *disturbance of internal oscillators and their communications*. Thus, a homeopathic drug might be regarded as a small quantity of matter in which phase oscillating elements could coherently transmit oscillatory frequencies, via resonance, to both oscillating and non-linear biological fluids or complex 'metastable' structures (macromolecules, protein different conformations, membranes, filamentous structures, receptors).

### The 'Simile' as Heuristic Principle

In synthesis, the homeopathic simile can be re-evaluated as a heuristic (finding) principle, a principle of biological and clinical research which assists in finding therapeutic strategies: in classic homeopathy, the 'similars' are those compounds which generate symptoms akin to those of the disease in all of its pathological, psychological and physiological complexity. The administration of the remedy to a sick organism would restore synchronism and cooperativity in cell enzymes, metabolic cycles, molecular feed-back loops, bioelectric potentials, with the consequence of higher cooperativity and more efficient energy handling.

The two approaches to system regulation—scientific/reductionistic and homeopathic/holistic—are not conflicting, but use different approaches: mainstream pharmacology applies a 'structural' analog, which is identified as the molecule binding to specific receptors or enzymes of the target system (if known). Classic homeopathy applies a 'functional' analogue, which is identified as the diluted compound that is able to regulate and/or to trigger homeodynamic systems. This kind of functional analogy, based on the similarity of symptoms, can be exploited even if the details of the receptors or the effector enzymes are unknown within the complex homeodynamic networks.

Mainstream pharmacology is much more precise when the exact mechanism of the disease is known, and specific drugs can therefore be administered. Homeopathy could be more effective when considering the complexity of the disease and subtle regulations. The homeopathic approach may be useful specifically because it does not



focus on the cause of the disease, but on the teleonomy of the patient's reaction. It is therefore not to be considered an alternative approach, but complementary to effective drug use.

For example, some people frequently become infected (primarily upper-respiratory infections) due to climatic change, cold weather, stress or contact with an infected person (in schools or hospitals). It is known that often there is no molecular or genetic explanation which fully justifies such an increase of susceptibility to infection. It is obvious that the immediate cause of the infection could be microbial, but it is also true that the whole 'terrain' plays an important role. Therefore, a more logical and effective approach is one where the focus is placed on complex response stimulation, a homeopathic cornerstone (6,7).

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