Appendix 2

Science and Homeopathy: From "Life Force" to Biodynamics and Biophysics

Introduction

Homeopathy raises a number of puzzles for the scientific investigator. Both clinical and basic research investigate homeopathic phenomena (effects of ultra-low-doses or high dilutions and phenomena related to the *similia principle*).

We have seen that in last ten years a number of studies have been done on cells and on animals, with findings that suggest that homeopathic drugs have specific biologic effects in different experimental models. Homeopathic principles and notably the *principle of similars* can be reevaluated in the light of modern biological, biophysical, and immunological knowledge. However, a complete theory of how homeopathic drugs may function in the body is still lacking. As a matter of fact, accumulating evidence of the consistent effects of homeopathic medicines on cells and on animals and humans is not sufficient to explain how this therapy works.

The reason for this gap in knowledge about the action mechanism of homeopathic medicines may be that the ultra-low-dose phenomena and the similia law cannot be fully understood by utilizing the reductionistic approach that is utilized for conventional, high-dose drugs. Experiments carried out on specific and small-scale models can explain and demonstrate the validity only of specific and small-scale hypotheses.

A rational approach to explaining the action mechanism of homeopathy should take into consideration three major aspects:

- the similia principle;
- the problem of dilution and dynamization of drugs;
- the homeopathic theory of health and healing.

These three aspects can be considered separately—especially from an experimental scientific standpoint—but they are strictly interrelated. A realistic interpretation of homeopathy reconciles the *integrated* view, which considers the complexity of the human being in all his or her components, with the *reductionist* view, which considers the single organ, cell, or molecular mechanism. In fact, there cannot be a contrast between the whole and the fragment that this whole contains, and therefore various medical approaches should be utilized according to which level of integration and which physiopathological mechanism(s) is the object of treatment.

Since homeopathy is a holistic approach, taking into consideration all the levels of organization of the body, in order to fully understand its possible action mechanism we need a shift of paradigm from reductionistic to complex approaches. This is not a denial of the importance of reductionism and of exact, Galileian science, but is a step further, enabling us place simple evidence into a wider, more global context. This vision of biology (and consequently of pathology) emerging from the front lines of modern science, will help apparently paradoxical phenomena claimed by homeopathy to be seen in a new light.

The "vital force"

Healing is a fact of everyday life: we heal from a wound, from influenza, from abscesses, from a common cold. Thanks to sophisticated biological systems, after most injuries, the state of health is restored spontaneously or with little medical help. This singular healing power of living beings led ancient medical investigators to conceive the existence in the body of something like a mysterious *vital force* that is ultimately responsible for subtle and unknowable biological mechanisms that regulate all the internal processes of the body and its reactions to external stresses.

According to Chinese tradition, the proper and dynamic balance of the vital force (referred to as *ch'i*) is responsible for the maintenance of health; the loss or derangement of the same force is associated with most diseases (*yin-yang* imbalance). One of the fathers of the Western medicine, Hippocrates (460–377 B.C.), called this healing principle *vis medicalis naturae* (healing force of nature) and advised doctors to take great care not to disturb it with inappropriate treatments. In fact, he used to recommend *primum non nocere* (most important, do no harm).

Hahnemann, the founder of homeopathy, adopted a markedly vitalistic standpoint: that the fundamental factor in a human being's state of health is the vital force and any disturbance of this dynamic inner principle is responsible for onset of disease, just as, conversely, the "restitutio ad integrum of the vital force necessarily presupposes the return to health of the entire organism."[1]

Paragraphs 29–31 of the *Organon* clearly define what Hahnemann meant by disease, i.e. "every disease (not entirely surgical) consists only in a special, morbid, dynamic alteration of our vital energy," whereas the pathogens are only trigger factors. "The inimical forces, partly psychical, partly

physical, to which our terrestrial existence is exposed, which are termed morbific noxious agents, do not possess the power of morbidly deranging the health of man unconditionally; but we are made ill by them only when our organism is sufficiently disposed and susceptible to the attack of the morbific cause that may be present, and to be altered in its health, deranged and made to undergo abnormal sensations and functions—hence they do not produce disease in every one nor at all times."[2] We are amazed at how concepts that have only recently been espoused by the modern sciences of pathology and immunology could be so clearly perceived and expressed over 150 years ago.

Today, after the scientific developments of last century, we have accumulated an overwhelming amount of knowledge regarding the components and the mechanisms of living organisms, from single cells to higher multicellular organisms. The concept of vital force seems obsolete and unnecessary for the description of biological phenomena, including healing. Even if the term "vital force" has not completely been erased from the scientific dictionary, being still used as a synonym for *bioenergetics*,[3] the vitalistic approach has been definitely overcome and the scientifically-oriented doctor now considers the body's natural healing power as a manifestation of the evolutionary development of homeostatic and adaptive functions of cells, tissues, and humoral biochemical systems.

However, in spite of enormous scientific development, our understanding of the healing process is still primitive and unsatisfying, particularly with respect to complex, multifactorial, diseases. Unfortunately, the positive restoration of normal homeostasis after a perturbation is not always the outcome. A number of external or internal pathogenic factors—biological, chemical or physical harmful agents, or errors of diet or lifestyle—can modify permanently or semi-permanently the health state of a person, particularly when these factors interact with genetic predispositions. Moreover, internal factors (i.e. HLA molecules, blood coagulation, oxygen radical formation, amyloid deposit, platelet aggregation and so on), are linked to the defense mechanisms that may amplify to counteract the external harmful agents and become self-damaging and aggressive factors. In these conditions, the "natural" healing power shows its limits, so that chronic or even progressive diseases may develop. The inadequacy of modern medicine in the management of a number of common diseases, and the increasing problem of drug-induced diseases dramatically demonstrates that medically-assisted healing is still far from completely effective. The ultimate reason for this weakness of mainstream science is that well-being and disease are complex phenomena, and as a consequence, knowledge of single parts is not enough for regulation of the whole.

We call *biodynamic* the study of the vital force, that is, of the behavior of complex systems whose interaction and organization are responsible for the healing power of the body.[4]

A complex system presents properties which amount to more than simply the sum of its component parts. This is the main property of complex systems, and not necessarily due to the existence of a number of different components. A complex system can be composed of only a few elements, but the interaction of components on one scale can lead to complex global behavior on a larger scale that in general cannot be deduced from knowledge of the individual components.

Clearly, an entire book would not be sufficient for a thorough analysis of the mechanisms involved in healing processes, whose investigation is the field of modern biomedical sciences like genetics, biochemistry, cell biology, immunology, neurology, molecular pharmacology, and so on. Table 1 is a summary of the main systems that are responsible for the natural healing power of the body.

TABLE 1 Some mechanisms involved in the healing process at different levels of biological organization

Molecular mechanisms
DNA repair after mutation
Inactivation of toxins by antibodies
Free radicals scavenging
Self-assembly of collagen
Detoxification by cytochrome-P450
Buffering capacity of fluids
Action of "defensins" and lysozyme
Fibrin formation
Heat-shock proteins (chaperonins)
Cellular mechanisms
Cell adhesion and movement
Membrane exportation of toxins
Free calcium homeostasis
Virus nucleic acid degradation
Nerve fiber regeneration
Phagocytosis of foreign particles
Bacterial killing
Tumor cell destruction
Bone resorption and deposition

Systemic mechanisms

Inflammation
Immune response
Organ regeneration and remodeling
Haemostasis
Neuroendocrine response to stress
Cytokine networks
Sympathic/parasympathic balance
Rest and relaxation
Healthy diet

Psycho-social factors

Changes in lifestyle
Exercise
Solidarity
Love
Prayer
Efficiency of healthcare systems
Patient-doctor relationship
Sharing of cultural knowledge

The last part of Table 1 includes some examples of events and phenomena that are not applicable to the organic sphere, assembled under the heading "Psychosocial factors." In fact, human biology (etymologically, the "knowledge of life") can not be reduced to chemical or mechanical factors, because the human being is an *open system*, whose health state—and therefore whose healing power—is dependent not only on internal mechanisms but also on interaction with its environment. In a holistic medical perspective, the *essential rules* of homeostasis and of healing are similar at the different levels of organization that one may take into consideration.

A synthetic view of healing mechanisms

The homeopathic remedies are said to stimulate the self-healing power of the organism. Therefore any theory of homeopathy requires the definition of the healing mechanisms that are involved in the purported therapeutic effects.

The phenomena and the mechanisms involved in healing processes can be described according to two fundamental standpoints. The first one, that we may call *analytical*, considers all the single phenomena occurring in

cells, tissues, and blood during the healing from damage. For example, we may investigate the molecular changes by which the integrity of the bone tissue is restored in the place where trauma broke a bone in two pieces; we may describe how an infarct heals with formation of a small connective tissue scar; how white cells, attracted by bacterial products, leave the bloodstream and migrate into the tissues where they phagocytose and kill invader microbes; or how liver cells regenerate after severe intoxication or viral infection. In these and many other healing processes, a number of molecular transformations, cell growth cycles, and metabolic modifications are activated in a specific and restricted way.

The second perspective, which we may call *synthetic*, is to try to design working models by which the *fundamental principles* and the *logic* of a complex phenomenon such as the healing process can be studied and understood. For example, we may observe that healing from trauma or from infection is due not only to local factors, like coagulation, cell chemotaxis, and angiogenesis, but also to the participation of general factors, like activation of the hypothalamus-hypophysis-adrenal axis, production of cytokines that reach all the body through the bloodstream, changes of liver protein metabolism, and so on. It is a crucial aspect of the healing process that billions of cells act in concert and in a finalized manner in order to destroy foreign invaders or tumor cells and to reestablish the healthy morphological and functional state. To achieve this coordination, soluble hormones, nervous system, cell-cell interactions and possibly long-range signals such as electromagnetic signals provide a link between general, systemic, factors and local factors.[5] The reciprocal influence of systemic and local factors is so important that a psychological stress can be associated with immune suppression and infection, while, conversely, an infectious process under a tooth can cause profound psychological depression.

A further point that is connected with the synthetic approach is the *topological* problem. This term designates the study of the position that living matter takes in space. Analysis can provide information on the *composition*, but says little about the mechanisms of development and of restitution of the *form* in a tissue. These latter, in fact, depend on a number of factors, the most important being the *self-organizing* capacity of an assembly of several different types of cells, which undertake a number of reciprocal interactions.

Both types of knowledge of the healing process, the analytical and the synthetic, are important in order to describe and, possibly, to positively influence the healing process, but here we will give a greater emphasis to the second one essentially for two reasons: first, that a thorough analysis of the biological events involved in a single healing process (for example,

wound healing, bacterial killing, immune defense development, and so on) is impossible in the available space for this review; second, and more important, while the analytical approach has been intensively pursued by molecular biology in the last three decades and represents the main body of teaching in medical schools, the synthetic perspective has been and is almost completely overlooked by modern, high-tech, medicine.

Systemic thinking or *integrative thinking* is profoundly rooted in the history of physics and of mathematics in the twentieth century, representing a kind of reaction to the mechanism of the nineteenth century. The changes occurring in these sciences, in turn, prompted the development of cybernetics, informatics, ecology, and also of biology.[6] In the history of medicine, a global approach to human health and disease has received much more attention by so-called complementary medicines, which are characterized by a holistic standpoint and developed before the modern western scientific (often reductionistic) paradigms and in some case independently of them. Therefore, a rethinking of the general principles of the healing processes may serve both as a stimulus to new scientific research in the conventional, mainstream, field and as a key to understanding in a deeper and more rational way the basis of other medical traditions.

For over twenty years we have investigated the biochemical mechanisms of microbial killing and, in general, of the inflammatory process, which undoubtedly represents the first and the main biological mechanism of healing. The need for further progress in this field, combined with the admission of the overwhelming complexity of the problem itself, are the main reasons that led our research group to think about the mechanisms involved in the healing process from a holistic perspective. Our goal is integrating the current analytical approach with the possible contribution of the "science of complexity," of chaos theory, and of traditional medicines.[7] The study of homeopathy was of great inspiration and help in this integrative work. (Further discussion on the problems of pluralism in therapeutical methods, of different medical paradigms, and on the prospects for their integration, particularly as concerned with homeopathy, can be found earlier in this book.)

Biodynamic properties of living systems

Healing and life are two faces of the same coin. We can not properly understand the former without a definition of the latter. Therefore, here we will examine some essential features of living systems and of their pathological aspects. Understanding the pathogenesis of disease is a fundamental requirement for the comprehension of how disease can be reversed,

either spontaneously or with medical help, and a person's health be brought back to a normal state.

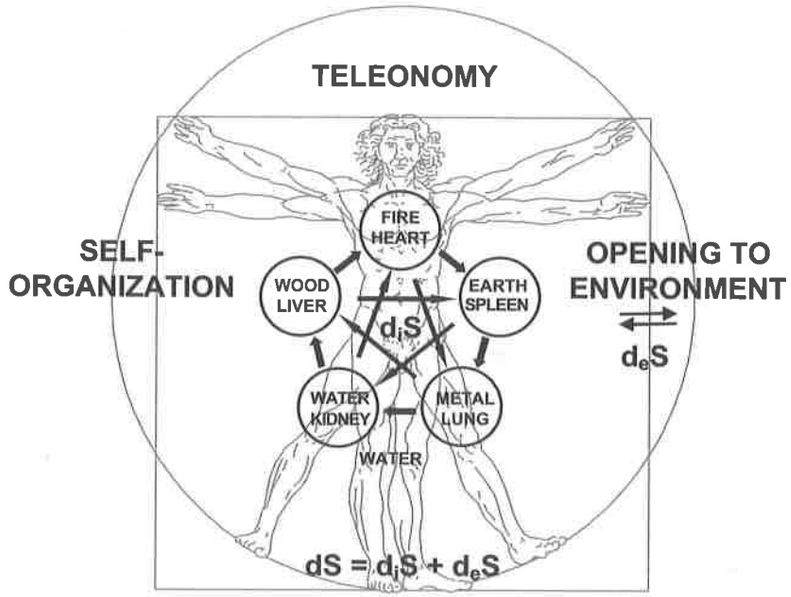

FIGURE 1 General Properties of Living Systems

The essential features that allow the birth, growth and development of life, and that include the healing capacity, are essentially two: *self-organization* and *openness* to external regulation (Figure 1). Moreover, these two features have a scope (teleonomy), that is the life of the individual, the best adaptation to the changing conditions, the survival, the healing, the reproduction, the development of human consciousness. Here is the *biodynamics* in modern terms.

Self-organization is based on the existence of multiple elements (ions, molecules, molecular aggregates, cells, organs), that are linked by multiple and reciprocal interrelations by which continuous quantitative and qualitative changes occur. A multiplicity of elements connected by physical forces, in suitable conditions and when they are subjected to a flux of energy (heat, light, mechanical agitation, etc.), tends *spontaneously* to organize as a *system*.[8] (We mean by the word *system* any organized whole of many elements.) *Organization* means the existence of a "structure" (either spatial like a *form*, or temporal, like a series of events occurring with a

given *frequency*). The structure, therefore, is the existence of a state of organization (order), a state that is different from pure chance (disorder).

Many systems have been described as being capable of generating some kind of organized structure starting from a more disordered assembly of many constituents: the order may be spatial (waves, spatial structures such as rings or spirals) or temporal (oscillations, cycles, rhythms, pulsations). Often these ordered and dynamic structures can be found in biological phenomena but also in experimental chemical or physical systems. There are even chemical reactions that are capable of self-organization in nonequilibrium states in the course of time. The prototype of these reactions is the one described by Belusov-Zabotinskij: in this reaction, the reagents (we will ignore the details) generate a colored product which, however, is not always constant, nor always on the increase, but continues to oscillate in the course of time, thus giving rise to talk of a *chemical clock*.[9] Another typical example is represented by the formation of convection Bénard cells in water exposed to a flux of heat.[10]

One of the main outcomes of self-organization is the formation and maintenance of *structure*. In cells, structures have absolutely indispensable functions: we need only mention the cell membranes, which divide the cells into compartments and separate the cell itself from the surrounding environment. Through the membranes a marked *disequilibrium* of substances and electrical charges is maintained, which is necessary for a whole series of functions, such as the production of energy (mitochondria), the production and transmission of signals (neurons), and the activation of movement (muscles).

If orderly systems are formed in space (e.g. circles, target-type structures, spirals) this means that each element is affected in its position and speed by the others in the system: it takes its "orders" or information from the adjoining element and behaves accordingly. This results in phenomena of cooperation and coherence, so that the elements arrange themselves in orderly structures. If orderly structures are formed in time this means that the state of the system in any given instant *depends* on the previous one and *conditions* the next one in the series. In brief, it has been claimed that it is the very appearance of *space-time organization*, due to *broad-ranging* interactions among the elements of a system, that constitutes the most typical feature of *complexity*.[11] In other words, complexity contains not only a quantitative factor related to the number of elements involved, but also a qualitative factor associated with the appearance of *structure*, or *form*.

As a first and broad generalization, we may say that differentiation and development coincide with the expression and maintenance of a structure and with efficient storage and handling of the energy flux, while disease

and death coincide with the loss of structure and dissipation of information. In order to efficiently handle the energy flux, living systems require *information*. (The word *information* refers to the special kind of energy that is required to maintain the order.) This information is present *inside* the organism from the beginning in the embryo, both as genetic (DNA) and epigenetic (other space-temporal structures that influence the DNA expression of specific genes) and penetrates from the environment as a number of signals that are perceived by specific receptor structures.

In the behavior of complex systems the *quality* of the information is far more important than the quantity, or the energy consumed to provide it. The biological system, in particular, has developed and has integrated within itself the systems of production and use of energy, utilizing various well-coordinated metabolic pathways and the rapid availability of phosphorylated intermediates. The functional reserve of these systems is considerable (except in highly pathological cases of cell damage or anoxia), so that normally the functional oscillations and the behavior patterns of cellular or organic biological systems do not depend on addition or subtraction of energy, but on control mechanisms at the *information* level. The more complex and "flexible" a system is, the scantier may be the amounts of energy capable of altering its behavior. We need only mention, for instance, the brain, which is in all probability the most complex system existing in nature. It can be mobilized—and, as a result, so can the entire body—by nonmolecular stimulations, which in a certain sense may be devoid of energy or matter. Another example is provided by molecular biology: DNA, where highly significant biological information is stored, may be changed even in a single base of the billion base-pairs of which it is composed, and this minimal change can cause a fatal disease.

The latter point brings us to consider the flux of information to which a living system is constantly exposed. Besides being endowed with self-regulating properties, it can be seen also as an *open* system, i.e. a system that is dependent from the beginning on the environment. Thus, self-organization does not mean that such an admirable capacity of increasing and maintaining complex forms and functions can occur independently of external help. On the contrary, the thermodynamic stability of a system is guaranteed by the continuous exchange with the environment. As a mater of fact, life itself, and healing in particular, can occur only because living systems are open systems (also called *dissipative structures*).

The second law of thermodynamics can be formulated briefly as follows: every *isolated* system, where any kind of transformation takes place, is subject to a series of processes tending to move from a very improbable state (that it is in) to a very probable state associated with the ensemble,

where each transformation is associated with increase of *entropy* (disorder). To prevent this drift toward equilibrium, to move the system and each sub-system back toward the improbable state, work has to be constantly performed. All the vital activities of living beings that underlie differentiation, development, growth, reproduction, and healing are processes that occur far from equilibrium, a condition that can be maintained by a continuous stream of energy, matter, and information. "Any creature cut of from contact with the stream dies by asphyxiation or starvation. Structures and complex molecules come unglued, motion ceases, gradients dissipate, order decays; equilibrium is death."[12] Life implies holding out against equilibrium, converting energy into organization, and these things are possible only at the price of continuous work and continuous expenditure of energy.

The laws of physics and chemistry constitute boundary conditions that living systems must obey, but they do not usually determine which choice is performed in order to maintain and restore organization (survival and healing). Therefore, biology cannot be reduced to chemistry or physics, and to understand life other distinguishing properties have to be considered. One of these properties is the *teleonomy*, which designates the purposeful character of living things. The machinery of life *uses* the laws of chemistry and physics and the available energy (in first and fundamental instance, the sunlight) *in order to* (i.e. with the purpose to) maintain the complex organization of life itself. This purpose is evident in the evolutionary design and in the developmental behavior of each living being from zygote to adult organism.

The teleonomic character of the machinery of life is indisputable, and is documented also by the precision with which the organism tends to reintegrate its original structure after an injury. Each living system is endowed, right from the outset, with a *project* and most of its activity is used to assimilate energy and matter from the outside to match this project, notwithstanding all the perturbing factors. However, development is not *unconditioned* and the project is not pursued without problems, because the structure and function of the living organism are flexible and may *adapt* to the environment. In the proper balance of conservation of structure, adaptation is the key to healthful life.

The teleonomy of the vital force was suggested also by Hahnemann himself: "In the healthy condition of man, the spiritual Vital Force (autocracy), the dynamic that animates the material body (organism), rules with unbounded sway, and retains all the parts of the organism in admirable, harmonious, vital operation, as regards both sensations and functions, so

that our indwelling, reason-gifted mind can freely employ this living, healthy instrument for the higher purpose of our existence."[13]

Time-dependent organization (rhythms)

We have seen that an organism is nothing if not *organized heterogeneity*, with nested dynamic structures over all space-time scales. Organized heterogeneity can be envisaged both on spatial and temporal scales. Spatial differentiation of the body into organs, tissues and cells is a familiar concept. The cell is partitioned into subcellular *organelles* and *compartments* separated by membranes. Molecular and electrical signals are unceasingly and rhythmically exchanged between these compartments. Within each compartment, local circuits of macromolecular *complexes* or of single enzyme proteins can be identified as responsible for cycling energy transformations or for storing biological information. Moreover, inside each sufficiently complex molecule (e.g. a protein), several *domains* can be described, whose function is to catalyze chemical reactions or to allow interaction with other molecular or electrical signals. Conformational changes of these flexible molecular structures enable proteins to absorb energy from the site where it is released, store it, and deliver it to other structures. Therefore, spatial differentiation and signal communication in living systems spans at least ten orders of magnitude, from 10^{-10} m for intramolecular interactions to meters for nerve conduction and blood perfusion in the whole organism.

Temporal organization of biological phenomena is evident in the rhythmic functional modifications of cells, tissues, and organs. These oscillating mechanical, chemical and electrical events range from 10^{-14} s for resonant energy transfer between molecules to 10^{7} s for circannual rhythms and to even longer periods if one considers population dynamics. Physiological variables such as enzyme reactions, neuronal activity, heart rate, respiration, cell division, ovarian cycle, corticosteroid circadian variations, cell calcium oscillations, membrane polarization/depolarization, sleep/waking, oxidative metabolism, actin polymerization, cyclic nucleotide concentration, all undergo time-dependent oscillations. Periodical variation of molecular concentrations can be used, by living systems, as means for coding and transmitting information.[14] In other words, signals can be transmitted and perceived not only as variations in the *amplitude* of the intensity of a given phenomenon, but also in the *frequency* by which they occur. The most familiar example of *frequency-modulated* signal transmission is the action potential in the nervous system, but recently other molecular

oscillations such as calcium waves and hormonal changes, have been interpreted in this new light.[15]

Oscillations of the control parameters of the various physiological systems are the norm in biology and medicine. If, however, the coordination is lost, i.e. the *connectivity* of the system as a whole and in relation to the rest of the body, certain subcomponents may oscillate in an excessive, unpredictable, and pointless manner, thus generating localized disorders which may, however, be amplified (the amplification of fluctuations is a typical behavior of chaotic systems). Oscillation thus becomes disorder and takes on the aspect of disease, in that it causes the emergence of substantial symptoms and damage. In a complex system, loss of communication means pathology.

A complex system is regulated by communication modes suited to the degree of complexity. For example, communication between two molecules (fairly simple system) consists of electrostatic attraction or repulsion; communication between several groups of molecules (complex system) consists of undulatory dynamics and spatiotemporal variations (oscillations of particular signal molecules); communication between organs and systems is entrusted to further complex systems which use both chemical (hormones, cytokines) and physical (action potentials and probably acupuncture meridians) methods of communication. Communication between different individuals is achieved by other methods such as words, writing, looks, and broadcasting by cable or over the air. This means that if we want to "enter the communications network"—with a view to understanding and eventually influencing it—we have to use the same method or methods of communication as the system we are interested in. If a system is regulated by modes of communication consisting of synergism between several molecules acting at low doses, to enter this network in an effective way theoretically we would need to use the same method: low-dose modulators exploiting synergism and antagonisms. If, on the other hand, we use modulators of only one molecular type and at high doses, we obtain effects, admittedly, and even effects in the desired direction, but not effects in complete harmony with the system itself, resulting in a high incidence of unwanted side effects.

Analogy

In order to deal with puzzling issues like those of self-organization and regulation of biological healing, one may take advantage of cybernetic models that utilize the language of mathematics. On the basis of these models, *analogies* can be drawn with physiological phenomena, trying to understand how these mathematical concepts can be applied to living systems. What is meant by *analogy* is similarity between two distinct systems one of them to be better understood on the basis of knowledge already gained about the other. Analogy can therefore be used to construct more advanced models compared to those in current use and to make forecasts about unknown systems starting from known systems (usually physicochemical or mathematical) which act as archetypes, i.e. as *reference systems*.

The analysis proceeds in two steps. Firstly, certain analogies are traced between the observations and the behavior of physicochemical reference systems. This defines the type of model that is likely to be the most appropriate representation of the system concerned. Then an attempt is made to go beyond the stage of plain analogy, to pinpoint, within the framework of the model adopted, the specificity of each problem and to incorporate it in the description. Lastly, the predictions of the analysis are compared against experience with past behavior, and, assuming an agreement is reached on quality, these predictions are used to foresee future tendencies.

Of course, drawing an analogy does not provide the final proof of the quantitative correspondence between the model and the natural object, but analogic reasoning is a potent instrument that proves very useful in understanding complex objects and situations. Analogy is useful in order to construct hypotheses regarding complex phenomena on the basis of the knowledge of similar, more simple, phenomena that are better known. Therefore, analogic reasoning, when coupled with testable hypotheses, is integral part of the scientific proceeding when it comes to describing and understanding complex systems.

We know how important analogy is for homeopathic methodology.

Models of dynamic systems

The contribution made by the physico-mathematical approach to the problem of complexity is much greater than might be imagined: while it is true to say that a living system with its thousands of subcomponents will never resemble a chemical system with two or only a very few components, and can never be described by a mathematical formula, on the other hand, it is also true that the study of the complexity of "simple" systems may enable us to discover *basic rules* of behavior which are repeated in substantially identical forms in systems with a different evolutionary status. It has been suggested that a complex, nonlinear feedback system is something like *a universal formula for life*,[16] because it summarizes, admittedly in a very general way, most of the processes of life.

The mathematical formulation of feedback essentially describes the dynamics of a mechanism operating in living beings. As we have seen, living systems, in fact, are regulated by reaction and counteraction cycles that constitute so-called *homeostasis*. These cycles are nothing more or less than the repetition of the same operation (by analogy with mathematical iteration) in which the result of the previous cycle serves as the basis of the next one. For example, at the end of the systole-diastole cycle the heart reverts to the end-diastolic condition; at the end of a mitotic cycle the condition of the two daughter cells becomes in turn the starting condition for a new mitosis; thus, every rhythmic modification of the organism hinges upon the previous state and occurs according to fixed rules. (In the analogy we have adopted, the rule is the mathematical formula.)

The state of a dynamic system at a certain time can be seen as a point in the *space of phases*, i.e. in the space delineated by the variables of the system itself. For example, the localization of a point in a three-dimensional space is described by the value of the three (x,y,z) orthogonal axes. The dimension of the space of phases can be less or more than three, according to the number of variables of a given system. When the dynamic of the system is also considered, i.e. taking into consideration the variable of time, the evolution of a dynamic system in space-time can be also seen as series of points (a line) that follows a *trajectory*. Starting from different initial positions in the space of phases (different initial conditions), the same system may describe different trajectories that converge to a single point (so-called *point-attractor*), or trajectories that "visit" the same points (also called *orbits*, or *periodic attractors*), or finally trajectories that explore the space of phases in a way by which they never repeat the same path. The latter situation, where no regular periodicity can be seen in the system behavior, is also referred to as a *strange*, or *chaotic*, *attractor*.

Biological complexity and chaos

In recent years, considerable attention has been given to the fact that in healthy living systems all the physiological variables oscillate according to rhythms that are neither completely periodic nor totally random. These dynamic oscillations respond to complex and coordinated control systems that comply with the "laws" of deterministic chaos.[17] Introduction of chaos theory into the biological domain has a number of implications of both theoretical and practical value.

First of all, it should be pointed out that deterministic chaos is not randomness but *pseudorandom noise* or *low-dimensional aperiodic signal*.[18] While the classical phenomenological definition of chaos means absence of order

(state of maximum entropy), the modern definition is based on nonlinear mathematics, whose principles were anticipated during the late nineteenth century by Poincaré and rediscovered by Lorenz in 1963, discussed in a paper with the title "Deterministic nonperiodic flow."[19] With the use of modern electronics, the mathematical analysis of chaos has developed to a point where it is beginning to have an important impact on a wide variety of fields including biology and physiology.

An important characteristic of a chaotic system is referred to as *sensitive dependence on initial conditions and to perturbations*. Sensitivity in this case refers to the situation in which two similar systems are started initially with variables having very close values but following this, their dynamic states diverge from each other quickly. Small differences in initial conditions or small perturbations produce very great differences in the final phenomena, suggesting the impossibility of long-term predictions.

Another way by which this phenomenon is exemplified is the so-called *butterfly effect*, the principle conveyed by the dictum that the flapping of a butterfly's wings in Brazil may trigger off, or stop in its tracks, a tornado in Texas.[20]

On the other hand, this also means that small applied perturbations can control chaos,[21] provided that these perturbations are specific and delivered at the right time-intervals. As stated by Elbert, "in the future it may even be possible to devise therapies for disease by manipulating control parameters back into the normal range."[22] The subtle communications between oscillators, which generate synchronism and cooperativity, are of paramount importance in many physiological functions. Regulation of these physiological and biochemical events could be possible through exploitation of the "rules of chaos," and this may have importance for the interpretation of the effects of low-energy or low-dose medical manipulations. Even signals which are extremely small, but which are endowed with highly specific information and are capable of resounding in unison with the recipient system, could act as regulators, if it is admitted that the deregulated system or systems are in a state of precarious equilibrium, near to the *bifurcation point*, where the choice whether to move in one direction or the other is related to minimal fluctuations on the border between order and chaos.

Another important example is provided by the cytokine network, which exhibits nonlinear behavior.[23] Such nonlinear cytokine interactions have important implications because they may give rise to unexpected or counterintuitive effects, that are not always recognized or taken into account in therapy. In inflammatory diseases (such as rheumathoid arthritis, multiple sclerosis and so on), inadequate immunosuppression may make

things worse by inducing high-level of pro-inflammatory cytokines. So, in the context of cytokine networks, the goal of a therapeutic strategy would be not to change the concentration of one or few cytokines, but to move the whole network from one state-attractor to another (say from an inflammatory response to a noninflammatory one). Thanks to the *rules* governing chaotic systems, this could be done by using small carefully controlled interventions, rather than high doses of chemical drugs. Of course, in order to have any hope of doing this, one needs to understand the dynamics of the whole network far better than we do today.

The new concepts emerging from chaos studies tell us that at this "border" minimal variations in the conditions of the system (such as those induced even by a very small oscillatory resonance) may play a decisive role in the subsequent evolution of the system itself. In a variety of systems, the "butterfly effect" may be used to control chaos, on condition that the parameters to be controlled and changed are well known.[24]

The phenomenon of resonance is well known in physics, where it occurs in many fields: acoustics, mechanics, and electromagnetism, as well as nuclear physics. By virtue of this phenomenon, a system that is characterized by its own oscillation frequency can enter into vibration if stimulated (subjected to sound waves, electromagnetic waves, or mechanical vibrations according to the nature of the system) by frequencies close to those peculiar to the system itself. If the system is already oscillating, the resonance may greatly increase the amplitude of the oscillation, whenever the waves overlap, while the opposite may also occur, namely an arrest of oscillation, if the interaction is between two waves of the same frequency but opposite in phase.

Resonance, then, is a means whereby information is transmitted between two *similar* systems (as regards vibrational or harmonic frequencies) without the passage of matter. These linkage phenomena between oscillators, which generate synchronism and cooperativity, are of paramount importance in many physiological functions, particularly in the nervous system, but also in the cells regulating cardiac rhythm, in the cells secreting insulin in the pancreas, in the ciliated epithelia, and in the involuntary contractions of smooth muscle. Interestingly, it has been suggested that resonance may transduce information between an oscillating, low-level, electromagnetic field and molecular sub-domains of cell enzymes.[25] This type of interaction should lower the activation barrier of the rate-limiting step of enzymic reactions, thus increasing the overall catalytic activity.

Order and variability

The physiological variables controlled by the homeostatic systems oscillate continually between a maximum and minimum allowed value, but this variability may be more or less regular or rhythmic, depending upon multiple conditioning factors performing the various control functions. On changing the rate by which these transformations take place, abrupt changes between periodic and chaotic behaviors (and visa versa) are possible.

Thanks to the development of deterministic chaos theory, some processes formerly perceived as erratic, are now viewed in terms of pattern and lawful relationship. Chaotic phenomena underlie the idea of structure and the potential for describing complex systems, rhythms, shapes, and behaviors with the aid of relatively simple formulations. If an apparently random phenomenon reveals, by this mathematical analysis, the features of a chaotic phenomenon, its behavior can be better predicted and manipulated. The rate of enzymatic activities oscillates when two enzymes compete for the same substrates, and small changes in concentrations can lead to changes in the frequencies and amplitudes of oscillations, causing them to become chaotic if previously harmonic or to become harmonic if previously chaotic.[26] Analysis of temporal variations in hormone levels in healthy subjects has revealed chaotic situations in this area, too.[27] Other applications of the theory of chaos have been described in cardiology. For example, it has been reported that the heart rate of a healthy individual varies over time with an intrinsically chaotic periodicity.[28] Obviously, these are not arrhythmia, but oscillations in normal rhythm. The electroencephalogram also shows similar chaotic patterns as normal aspects of its functioning.[29]

Many, if not most, of the physiological rhythmic phenomena in healthy individuals show chaotic dynamics, and nature uses chaos in order to increase variability, flexibility and adaptation. In complex systems like heart and brain, a decrease of chaos means disease and predicts serious pathology like cardiac arrest or epilepsy.[30] In the immune system, too, chaos may play a very important role, especially because this system continually needs to generate new forms of receptors to cope with all the possible antigens that the outside world and the inside of the body may present. *Fantasy*, then, is a fundamental property of the immune system, without which the body would lack the necessary adaptability to a world in a constant state of change and the ability to defend itself against potential aggressors.[31]

Systems with mixed feedback (both positive and negative feedback) and multiple feedback with different time constants are sources of deterministic chaos. This is the case of the whole organism and of the whole cell,

which can be described as dynamic systems where the *equilibrium* is a special case of attractor, the integration of a number of attractors. 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.[32] Rapid state changes and bifurcation are characteristic of networks that are sensitive to very weak initial conditions that lead to widespread changes in the whole system.

Networks

A peculiar property of complex systems is the ability to evolve over the course of time. This is observed both in the biological development of any organism (ontogenesis) and in the development of living species in general throughout history (evolution). In the classic Darwinian theory of evolution, the emergence of increasingly complex species is the fruit of *random variability* and *selection*, which operate to the advantage of those species which, by virtue of characteristics acquired by chance mutations, better succeed in adapting to increasingly difficult environmental conditions and in surviving the competitive struggle for vital space and food. This well-known concept of natural selection and the survival of the fittest in evolution has also been applied on a molecular and cellular scale as well as in embryology. The classic view of the origin of order and diversification of biological species—based on natural selection—has recently been contested on the basis of mathematical studies and computer models showing that, alongside natural selection, other mechanisms are involved, which have been grouped together under the term *self-organization*.[33]

As a result of the laws of chaos, nonlinear dynamic systems can easily present transition from order to disorder and vice versa, following even only minimal perturbations in control parameters or in the energy flow across such systems. Nevertheless, in these cases, we are invariably in the presence of changes somehow induced from the outside. There may, however, also be a phenomenon whereby the complex, disorderly system spontaneously "crystallizes" in an orderly state. From disorder to order thanks to *an intrinsic original property* of the system itself and with no input of outside energy; quite rightly, this phenomenon has been termed *antichaos*.

The mathematical models of self-organization were initially developed with the aim of explaining how the cell genome is organized. The genome can be viewed as a complex computer in which there is a data memory (information stored in the DNA for approximately 100,000 different proteins), but also the parallel processing of some of this information (a few hundred or a few thousand data units simultaneously). What is more, many

of these protein data units influence the genome itself in its activity, in multiple control sites. In this way, many genes are coupled with the functioning of others, influencing one another reciprocally, and constituting a *network*.

Networks are complex structures because the state and the changes of each element depend, directly or indirectly, on the state and the changes of all the other elements. Therefore, a network behaves as a *coherent* system, whose health state is governed and restored depending on the connectedness of internal and external processes, that is by the value of original information, the capacity of signaling the harmful modifications, and the efficiency by which energy is channeled towards the purpose of reconstructing the original conformation.

The coordinated and sequential behavior of this network is the basic factor responsible for the functioning and differentiation of the cell, with the result that a liver cell is different from a heart muscle cell and performs different functions, despite containing the same genetic information, being composed of the same elementary materials (amino acids, sugars, lipids, carbohydrates), and obeying the same "general functioning rules" (biochemical reactions).

The concept of network is useful for describing a general organization model of complex systems:

- society: network of individuals;
- body: network of organs;
- brain: network of nerve centers;
- immune system: network of cells;
- cells: network of molecules;
- molecules: network of atoms;
- atoms: networks of elementary particles.

According to the external and internal conditions (number of components and of communication pathways, temperature, chemical concentrations, rate of changes and so on), a network system may assume different states, or *attractors*. An attractor is the state or the series of states (pattern) to which the behavior of a system is attracted. It therefore possesses an important property—stability. In a system subject to perturbations, movement tends to be towards the attractor. The theory of dynamic system shows that the attractor may be a single point, as for example in the trajectory of a pendulum when it reaches the stationary state, or a finite number of points reflecting a periodic-type behavior (orbit), or an infinite system of points generating a figure in the form of an orbit which never repeats itself identically, as may happen in chaotic systems ("strange attractors").

The choice between one state (or attractor) and another possible state (or attractor) often depends on the "experience" to which the system is exposed. The modifications that the system has undergone, are "stored" in the space-time as specific permanent and semi-permanent structures, whose existence influences further development and subsequent responses of the system itself. Unlike what happens in a system in a state of reversible equilibrium on changing the external or internal parameters, in a complex system a situation can be reached in which there is a *symmetry breaking*, or an irreversible change. While it is true that random fluctuations and perturbations can usually be damped, beyond certain threshold values, or in the presence of appropriate environmental conditions, these effects are not annulled, but with the system acting as an amplifier, a reaction is triggered which removes the system from the reference state.

Changes of attractor represent a potential problem for the healing process because by this means a certain specific behavior or structural modification can become "fixed" to a pathological attractor due to a specific perturbation, losing the possibility of fully reversible modifications. This kind of pathological modification of a dynamic system can be considered an *erroneous adaptation*, where the system finds a fixed point or a periodically oscillating behavior outside the normal, original, range of variation. In a particular sub-set of the space-time, i.e. locally or for a short period, this new attractor may appear as the most convenient in terms of energy expenditure, but for the system as a whole and for the future prospects of development of the system itself, an erroneous adaptation can be highly deleterious. Something like this process can be envisaged in the transformation of an acute inflammation into a chronic reaction, or in the heart and blood vessel hypertrophy in chronic hypertension, or in the receptor adaptation that justifies the hyperglycemia in hyperinsulinemic type II diabetic patient. Also the tissue protein or lipid deposits that can be found in amyloidal diseases (including Alzheimer disease) and in arteriosclerosis may be seen as an adaptation of tissue homeostasis to a chronic load of pathologic precursors of these deposit moieties.

We have previously shown how the concept of *change of attractor* has implications also for the understanding of the action of low doses or high dilutions of drugs selected according to the principle of similarity, traditionally proposed by homeopathic medicine.[34]

Plausibility of homeopathic high-dilutions/high potencies of drugs

The new concepts emerging from complexity theory have profound implications on the ways in which patients and diseases are investigated and treated. Since we have done a number of experimental and theoretical studies on the putative mechanism(s) of action of homeopathy, we shall attempt here to summarize a few points regarding this particular field of complementary medicine. Of course, the following points should be underlined: a) hypotheses are essential to the evolution of knowledge, but one has to guard against presenting them as certainties; b) the following discussion is based on the assumption that highly diluted remedies prepared according to the homeopathic methods are endowed with specific information of biophysical nature (superradiance, water clusters, isotopic lattices, and so on), a highly controversial issue that is discussed in other sections of this book; c) here we restrict our consideration to the possible mechanism of interaction between high-dilution homeopathic remedies and the organism, that is only one of the various questions raised by the homeopathic approach; and d) a biophysical perspective does not exclude that many effects of low- and ultra-low doses of drugs are due to "conventional" molecular interactions. The hypotheses set forth here also refer to theories proposed by other authors.[35]

A new vision of matter and life is emerging at the frontiers of science, particularly from the fields of quantum physics and mathematical theories and research that have yet to be systematized. Organisms are seen as highly regulated, complex, dynamic systems that display a characteristic metastability around certain homeostatic levels. This metastability is the net result of continual oscillations, rhythms, networks, amplifications and feedback cycles. Living systems are "suspended" between order and chaos; they partake of these two fundamental characteristics of matter and exploit them in a manner designed to promote survival. We cannot see how these new perspectives can fail to have an impact on the new orientations and trends in medicine. Medical theory, methodology, and technology have always proceeded hand in hand with the general scientific theory and socioeconomic situations of the times.

On this basis, a hypothetical model of the possible action mechanism of homeopathic drugs can be advanced. The following hypothesis is formulated starting from the assumption that some type of structural or dynamical information storage actually occurs in water. This assumption is based on the preliminary evidence provided by biological and biophysical studies reviewed throughout this book and in Appendix 1.

From a biophysical standpoint, disease may be regarded not only as a functional or molecular-structural abnormality, as in the classic view, but also (and not by way of contrast) as a disturbance of an entire network of electromagnetic communications based on long-range interactions between elements (molecules, nerve centers, organs, to mention but a few) which oscillate at frequencies which are coherent and specific and thus capable of resonance. This would be a *disturbance of internal oscillators and their communications*. Our knowledge is still too scanty to say whether or not these oscillators can be identified with certain nerve centers in particular (the ability to oscillate at characteristic frequencies is typical, though not exclusively so, of nerve centers) or with the collective behavior of nerve centers and/or other tissues or cells. With regard to cell-to-cell and intracellular communication, biophoton research suggests the existence of extensive coherent fields of interaction in the visible range.[36]

If the disease process involves a disturbance of oscillation frequencies—and of the communications associated with them—it should be brought back to a state of equilibrium by means of *syntonization or tuning, i.e. by means of a change in frequency imposed by interaction with another oscillator.* According to this notion, the homeopathic remedy might act in the patient as an external guide frequency.

A potentized homeopathic drug might be regarded as a small amount of matter containing elements oscillating in phase (coherently), capable of transmitting these oscillatory frequencies, via a process of resonance, to biological fluids (in turn mostly made up of water), but also to complex "metastable" structures, subject to nonlinear behavior patterns and capable in turn of oscillating (macromolecules, a-helixes, membranes, filamentous structures, receptors). There would thus be the possibility of a link between drug frequencies and oscillators present in the living organism perturbed by the disease.

It is very likely that in the near future studies on fractals and on deterministic chaos will be applied to physiology and pathology to an increasing extent. In fact, if chaotic dynamics is a *normal* aspect of physiological processes, investigating this may furnish more complete predictive information for characterizing the therapeutic effects of various types of periodical stimuli (including physiological stress, acupuncture, electric pacing, psychotherapy, and so on), of pharmacological compounds[37] and of highly diluted homeopathic remedies.[38]

The pathogenesis of many diseases, at least in their initial phases, is characterized by communication defects arising in the complex networks of integrated systems (control of cell proliferation, immune system, equilibrium between pro- and anti-inflammatory factors, coagulation and fibrinolysis, and so on), for which models can be created like the Boolean networks. In a network in which many homeostatic systems (molecular, cellular, systemic) are interconnected, the information of the entire system "passes through" cycles (attractors) which have variable, fluctuating spatiotemporal forms, but which can always be traced back, in states of normality, to a harmonic pattern where the whole is viewed in its entirety, aimed at the survival of the organism with the least possible consumption of energy. If one or more elements in these networks is delayed, or loses its information connections (i.e. something snaps in the homeostatic system itself, or some erroneous adaptation process follows an external perturbation) a pathological process occurs precisely because disorder is generated, or rather the system goes over to another attractor. According to these models, the new attractor, regarded as "pathological" in the case in question, may be preserved even if the initial perturbation is only temporary. Under these conditions, one could speak of a *tendency towards chronicity*.

As a consequence, if pathology is loss of communication, healing is increase of communication, establishment of connections between different systems, integration of responses. Sometimes, healing requires external perturbations that remove pathological adaptations. The "science" and the "art" of the doctor are to help the natural, but often erroneous healing power by providing the right information for the extremely complex, unique, and open system that is a human being affected by some disturbance of its homeostasis. Since biological communication is frequency-modulated and all the transformation processes in the body are networked and correlated, the organism can be seen not as an ensemble of mechanisms, but, instead, as a playing orchestra. Different parts (instruments) are harmoniously linked because they follow a series of guiding-frequencies. All the parts of an orchestra resonate and communicate, thus contributing to the overall performance. If an important part (an instrument) breaks down or goes out of the rhythm, that constitutes a threat for the functioning of all the orchestra. In analogous manner, a correlation in the rhythms of functioning organs and of the frequencies of oscillating cellular processes is established and maintained in the body. Every change in these rhythms affects, more or less profoundly, the correlated functions and spreads to other structures triggering a homeostatic reaction whose main purpose is to save the whole harmony of the organism.

Extrapolating these concepts to homeopathy, it is possible to envisage that major changes in the homeostatic systems and eventually the healing of the entire body could be obtained through light but carefully selected

stress such as inserting a needle into an acupoint, administering a low-dose remedy, or even providing the right psychological advice. Signals which are endowed with highly specific information and are capable of specific interactions with the recipient system, could act as regulators, if it is admitted that the deregulated system or systems are in a state of meta-stability, or precarious equilibrium, where different behaviors (attractors) can be followed and where the choice whether to move in one direction or the other is related to minimal fluctuations. Homeopathic drugs are thus thought to act as substitutes for an endogenous regulatory signal that, for various reasons, may be inadequate or ineffective because the system is no longer sensitive to it, being "blocked" in a pathological attractor by the disease itself. The traditional similia law presupposes that the intrinsic tendency to self-recovery can be supplemented and actively assisted by the employment of suitable stimuli to a system when it is in a specific sensitive state.

Despite all the limitations related to difficulties in rendering the homeopathic approach objective, it is clear that it entails an attempt to explore the patient's medical history at the level of the neuroendocrine system and thus to calibrate some form of therapeutic intervention at this level, too. Homeopathy regards inflammation as a *symptom* (i.e. as a signal or message) and not as a *disease*, and regards this symptom as the expression of an alteration of the relationship between subject and environment and/or between systems in the same subject.

The "secret" of homeopathy lies in the meticulous gathering of information both in the proving phase and in the homeopathic history-taking phase. This information can come from the hidden depths of the homeostatic regulatory system under investigation, but is still information. In the homeopathic method it is used directly in the therapeutic intervention, trusting in the fact that the body will know how to receive, decode, and utilize this informational input for the purposes of restoring the lost equilibrium. Another "secret" of homeopathy is that it deals with the human being as a whole, devoting the maximum attention to symptoms of a psychological type and those peculiar to each individual subject (individualization). In this way, it achieves a very substantial measure of specificity, inasmuch as it is now well known that the response to drugs can vary on the basis of the characteristics of the individual user.

Further insights into the analysis of symptoms

We integrated our experimental results and the resulting model with clinical homeopathic experience. This yielded a theoretical model of the similia principle based on observations of cellular and systemic homeostasis. The operating model used for reference is that of cellular and tissue stress with its phenomena of a) regulation and integration of the response to the stimulus, and b) of physico-chemical adaptations. These have several similarities with the so-called primary and secondary drug actions cited by Hahnemann.

Ultimately a careful analysis of symptomatology with an attempt to connect biological changes and the evolution of symptoms must be included in a discussion of the rule of similars. Our point of departure is the conviction that every symptom has its own significance and origin, which is almost invariably connected to biological changes (biophysical and/or biochemical), to the function and/or structure of protein molecules, cells, tissues, nervous center, and body systems.

One aspect of this definition ought to be considered: in explaining the law of similars Hahnemann uses the relatively original concept of the artificial disease produced by the medicine which should be capable of reducing the natural disease. Both Hahnemann's explanation of the law of similars and practitioners' clinical observations may be explained by our biological model and are curiously connected by it. Our model of the law of similars is based on the concept of homeostasis and biological communication. In this model homeopathy constitutes a reactivation of biological communication.

These hypotheses have the benefit of connecting our experimental observations with those of clinical homeopathy, for example, homeopathic aggravation, the return of old symptoms, the origin of symptom modalities, artificial drug-induced disease, the similarity and difference between pathogenesis and treatment.

The model we are using to better study the law of similars is basically that of classical feedback, where the points of regulation derive from the regulatory system ("RS") and from a variable "A" which oscillates between the two conditions "A/A'" in a reversible equilibrium. The model is presented in Figure 8 in this book and its implications for homeopathic similia rule are discussed in Chapter 6.

In light of the above, we need to consider how symptoms change in the acute phase (of alarm), and in the chronic phase (of adaptation). We have already mentioned that as a result of the decreased sensitivity of the RS

and its deficient response, disorder may continue in the absence of the pathogenic agent. At this point the system remains blocked in pathological behavior and is incapable of finding the original attractor associated with health.

The production of regulatory signal r is no longer integrated with the physiological circuit connected to variable "A/A'," but will depend on other signals connected to heterologous receptors. After adaptation and down-regulation, the level of factor r will follow other governing factors that translate into different and more characteristic symptoms.

Perhaps these events of priming and down-regulation occur dozens of times before the reserves of the organism are exhausted and constitute a true mechanism of pathology, i.e. appearance of chronic disease. When the dysfunction of the regulatory system impinges upon areas of marginal importance, other compensatory regulatory systems come to the rescue. However, if the dysfunction strikes in a region of central importance in the regulation, the alterations in these functions become functionally irreversible (pathologic adaptation). Here the homeopathic "simile" could help to recover the teleonomical functions of the RS.

As long as the organism has supplementary regulatory systems that can regulate the advancing disorder, probably only the mildest and most nebulous of symptoms will manifest. While these are of no great significance to conventional medicine, they carry weight in homeopathy. Examples include premenstrual headaches, acidic sweat, or sun intolerance. When finally many regulatory systems are in disequilibrium, true diseases will manifest in various tissues or organs.

Developing our hypothesis further we may place symptoms in various groups: a) direct or strong symptoms, which are related to the increase or decrease of a molecular signal, and are probably those which are more evident, immediate and perceptible and which transform a crisis into a disease (e.g. fever, pain, vomiting, hemorrhage, etc.), and b) complex or weak symptoms connected to changes in sensitivity and reactivity of the networks of regulatory systems.

In the latter group they are more complex, and while not being determined by a specific abnormal molecular concentration, are only of minor intensity and accordingly less felt by the subject. As they are governed by a large series of variables determined by the homeostatic network, they may only manifest under certain circumstances. But it is precisely for this reason that they are the richest in information because they provide a more complete idea of the current disequilibrium.

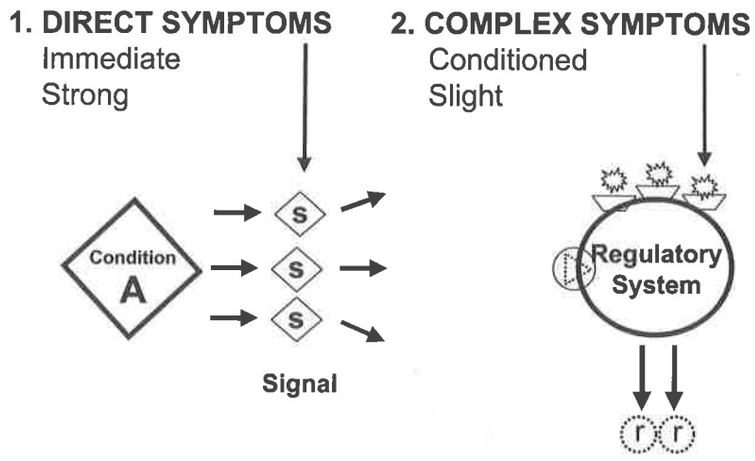

FIGURE 2 Two types of symptoms observed during the pathological phases. Symptoms due to increased quantity of molecules (i.e. fever) and symptoms due to change of system sensitivity. If our *in vitro* observations are correct, we should anticipate that in diseases where the endogenous signal is excessively stimulated, sooner or later a loss of sensitivity should occur, for example in diseases with an excess of inflammatory stimulation.

If our *in vitro* observations are correct, we should anticipate that in diseases where the endogenous signal is excessively stimulated, sooner or later a loss of sensitivity in one or more regulatory systems should occur, for example in diseases with an excess of inflammatory stimulation.

We have seen that symptoms almost always originate in biological (physico-chemical) changes in the structure and or function of enzymes, receptors, cells, tissues, etc., so the totality of symptoms of the body, of necessity, comprises all the functional and organic changes (tissues, cells, enzymes, or receptors) present within the organism.

Moreover, if we knew the correct hierarchy of symptoms and how to group them correctly, and if we knew "specific" medications for each of these possible groupings, then of necessity the appropriate utilization of such medications would address or modulate the microscopic disequilibrium connected to the symptomatology in question.

The specificity of which we speak could be viewed either homeopathically (law of similars) or as antidoting (law of opposites). It must be noted that the specificity of the drug in relation to the symptoms in question could be close only if the drug is capable of producing similar symptoms; otherwise the similarity would be significantly limited to a tissue or a cellular function.

This is due to the mechanism of divergence of signals and homeostatic networks that are regulated in a complex fashion and by agonist/antagonist couplings that differ from one tissue to another, as with subtypes of receptors to adrenaline, histamine, serotonin, and many other mediators.

If it is true, as follows from our hypothesis, that homeopathic modalities of symptoms are more connected to receptor sensitivity and homeostatic networks than to the action of high-dose molecular signals, the use and hierarchy of such symptoms would correspond to an indirect study of such sensitivity. And the difference between studying network sensitivity or molecular actions on the cell is quite different, because the latter is very similar to the action of an external drug, while the former is of necessity dependent on the body as a whole.

Consequently, a drug intended to regulate these types of symptoms (modalities) should address (in a more or less gentle fashion) such receptor sensitivities and their homeostatic networks. The hypothesis we propose is that the action of the drug on key-points of altered regulatory systems would force the cell or the system to recover the functional sensitivity which had been lost, including recovery of superficial receptors. This last idea is a fascinating hypothesis, as yet unconfirmed, to interpret the biological mechanism of the law of similars.

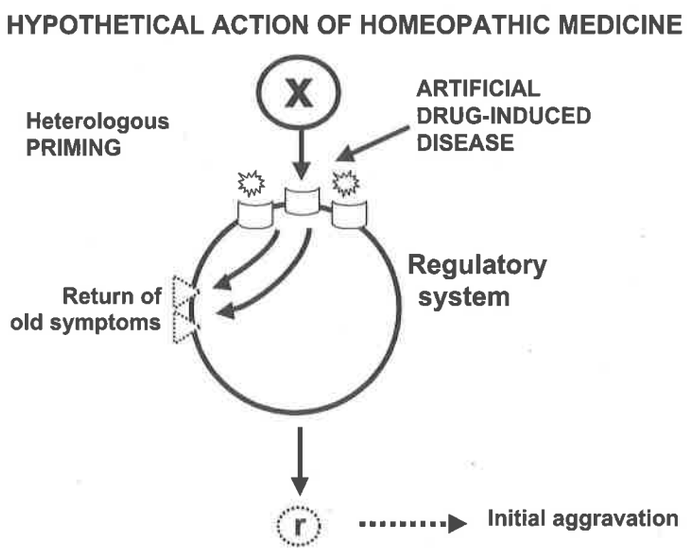

FIGURE 3 Some phenomena of the peculiar homeopathic healing response.

Could this idea be the corresponding phenomenon to Hahnemann's hypothesis in explaining the similia principle with the "artificial drug-induced disease"? If the true illness of a homeostatic system is the loss of communication, then true healing will be the recovery of this communication.

Thus, if our remedy acts on the stimulated receptors, the first effect to be expected is an increase in symptoms (initial aggravation) until this leads to a definitive change in regulatory receptors. Moreover, the possibility that the disabled receptor recovers its function would explain the repeated observation under homeopathic treatment of the return of old symptoms after an absence of years. In fact, given that the input signal has remained overactivated for a long time (years), the reactivation of receptors must lead to a reappearance of symptoms that disappeared when their function was lost.

Let us see where the rule of similars is situated according to this model.

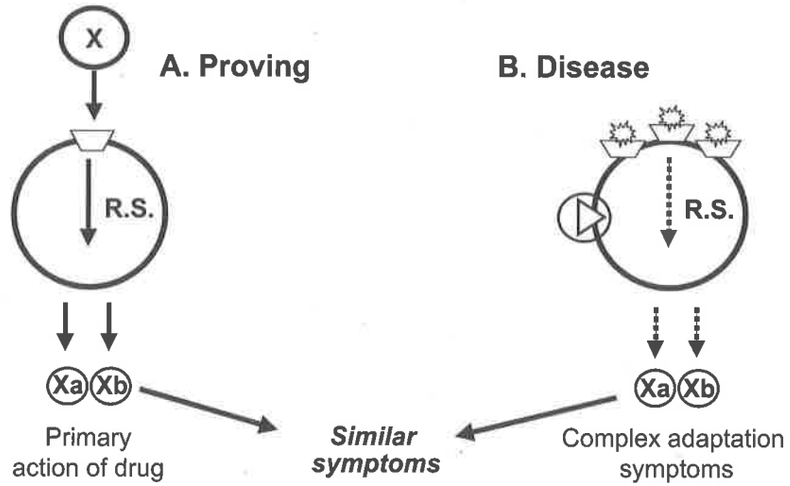

FIGURE 4 Biological hypothesis of the rule of similars.

As we see in A (proving), as a result of excessive molecular signalling, certain symptoms develop. In disease (B), desensitisation (down-regulation) occurs accompanied by heterologous hyperactivity. This determines a certain functional disequilibrium, accompanied by heterologous hyperactivity whose expression is other symptoms. Thus, we will observe two kinds of symptoms—direct symptoms (probably due to excessive quantity of molecules), and adaptation symptoms (probably due to cell hypersensitivity connected with network disequilibrium). The latter are the more interesting because they express the level at which the system is acting. These two

types of symptoms are quite different because they correspond to quite different pathways of biological communication. Moreover, direct symptoms, owing to their force, are poorly affected by modalities, those due to adaptation, and precisely because of their weakness, are more sensitive to modulation and to present themselves as a consequence of a particular modality.

If the doses used during homeopathic experimentation (proving) are quite attenuated, it is possible that the symptoms that arise may be due to an unknown physico-chemical phenomenon. This would be associated with an increase in sensitivity of the same receptors. The resulting onset of particular symptoms will derive from the modulation or integration of homeostatic networks for the action of low dosages on cellular targets. This is more than a hypothesis because the priming effect of low dosage substances is well- known, and we have seen experiments at very low dosage that confirmed it.

Coming back to pathological state (B), during a disease, symptoms similar to those caused by a particular drug could arise as a consequence of homeostatic adaptation during the chronic phase. In other words, the receptors in question should generate the same symptoms in their totality, either from hypersensitivity of the pathological state or due to hyper-modulation of homeostatic systems during experimentation. However, during experimentation symptoms are directly caused by the primary action of the drug. In pathology, the symptoms arise from the relative hypersensitivity of the same receptors as a complex result of homeostatic adaptation.

In simple terms the rule of similars in our model would exist between

a) *direct* symptoms (primary action) of experimentation; and

b) *complex* adaptation symptoms of the disease.

There are at least two advantages with this model: firstly, its biological bases are quite solid (priming and down-regulation); secondly, it leads to a sensible interpretation of several homeopathic phenomena such as initial aggravation and the return of old symptoms.

However, a limitation of our model could be the fact that we do not know if it holds true for all symptom groupings or is limited to those of the excitatory remedies, as it is more probable in our observations. Two more consistent objections to our model may consist in the lack of experimental proofs regarding the possibility that a) homeopathic dilution interacts with membrane receptors and that b) this action may invert the microscopic dynamic disequilibrium of homeostatic systems.

In proposing our tentative hypotheses we take heart from Claude Bernard's statement, that only by daring to make, and hopefully to verify scientific hypotheses, may human knowledge progress.

Summary

Our working hypothesis on the pharmacological action of homeopathic drugs could be summarized as indicated in the following points:

1. The *therapeutic similarity* of drug action may be fundamentally based on the widespread phenomenon of *inversion of biological effects* dependent on the *dose* and/or on the *physiological state* of the receiver.
2. Medicine that has been chosen according to the similia principle may be perceived by *specific* regulatory systems—that have a crucial role in the dynamic of the disease–as a *heterologous "similar" signal.*
3. Specificity of information may be based on the *sensitization* (priming) of the receiver due to biological stress, on the use of *ultra-low- doses/ high- dilutions* of medicines and on the *complexity* of the remedy actions at various levels.
4. The specific signal may trigger a homeodynamic reaction that shifts the global dysequilibrium of the ill person toward a *new dynamical attractor*, proximal to the healthy state.
5. In acute diseases, homeopathic regulation may be regarded as homeodynamic regulatory feedback, in chronic disease as *unblocking* of pathologic adaptation and orientation towards correct responses.
6. The clinical application of the similia principle (*symptom analysis in the complex field of the whole person*) may allow the identification of specific remedies even with the lack of detailed knowledge about the single molecular mechanisms of disease and of drug action.
7. The information of homeopathic medicines may have either *chemical* nature (ultra-low-dose) or *physical* nature (high-dilution/dynamization), or both.

References to Appendix 2

1. Hahnemann, C.F.S. (1994). *Organon of Medicine.* With explanations by Joseph Reves, edited from the 5th and 6th edition. Homeopress Ltd., Haifa, para.12.
2. Ibid., para 29–31.
3. Harold, F.M. (1986). *The Vital Force: A Study of Bioenergetics.* New York: Freeman and Company.
4. Bellavite, P. (1998). *Biodinamica: Basi fisiopatologiche e tracce di metodo per una medicina integrata.* Milano: Tecniche Nuove.
5. Endler, P.C., Pongratz, W., Smith, C.W., Schulte, J. (1995). Non-molecular information transfer from thyroxine to frogs with regard to homeopathic toxicology. *Vet. Hum. Toxicol.* 37: 259–260; Fesenko, E.E., Gluvstein, A.Y. (1995). Changes in the state of water, induced by radiofrequency electromagnetic fields. *FEBS Lett.* 367: 53–55; Goodman, E.M., Greenbaum, B., Marron, M.T. (1995). Effects of electromagnetic fields on molecules and cells. *Int. Rev. Cytol.* 158:279–338; Ho, M.W., Popp, F.A., Warnke, U. (1994). *Bioelectrodynamics and Biocommunication* Singapore: World Scientific; Adey, W.R. (1993). Whispering between cells: Electromagnetic fields and regulatory mechanisms in tissue. *Frontier Perspect.* 3: 21–25; Smith, C.W. (1989). Coherent electromagnetic fields bio-communication. In: *Electromagnetic Bio-Information* (F.A. Popp, U. Warnke, H.L Konig, and W. Peschka, eds.). Urban Swarzenberg, Munchen, pp. 1–17; Tsong, T.Y. (1989). Deciphering the language of cells. *Trends Biochem. Sci.* 14: 89–92.
6. Capra, F. (1996). *The Web of Life.* New York: Doubleday-Anchor Book.
7. Bellavite, P., Signorini, A. (1996). Pathologie, komplexe systeme, und resonanz. In: *Homoopathie und Bioresonanztherapie: Physiologische und physikalische Voraussetzungen Grundlagenforschung* (P.C. Endler, J. Schulte, eds.). Medizinverlag Maudrich, Wein, pp. 65–76; Bellavite, P. (1997). Disease as information disorder. *Advances—Journal of Body-Mind Health* 13: 4–7; Bellavite, P., Signorini, A. (1998). Pathology, complex systems and resonance. In: *Fundamental Research in Ultra-High Dilution and Homoeopathy* (J. Schulte and P.C. Endler, eds.). Kluwer Acad. Publ., Dordrecht, pp. 105–116; Conforti, A., Bertani, S., Lussignoli, S., Bellavite, P. (1998). Pharmakodynamik und komplexe Systeme. In: *Biologische Mediczin in der Orthopedie/Traumatologie, Rheumatologie* (H. Hess, ed.). Aurelia Verlag, Baden Baden, pp. 39–52; Bellavite, P., Semizzi, M.L., Lussignoli, S., Andrioli, G., Bartocci, U. (1998). A computer model of the five elements theory of traditional chinese medicine. *Complem.Ther.Med.* 6: 133–140.
8. Nicolis, G., Prigogine, Y. (1991). *La complessità. Esplorazioni nei Nuovi Campi della Scienza* Torino: Einaudi; Coffey, D.S. (1998). Self-organization, complexity and chaos: The new biology for medicine. *Nature Medicine* 4: 882–885; Kauffman, S.A. (1993). *Origins of Order: Self-Organization and Selection in Evolution.* Oxford: Oxford University Press; Kauffman, S.A. (1995). *At Home in the Universe: The Search for Laws of Self-Organization and Complexity.* Oxford: Oxford University Press.
9. Petrov, V., Ga'spa'r, V., Masere, J., Showalter, K. (1993). Controlling chaos in the Belusov-Zhabotinsky reaction. *Nature* 361: 240–243.
10. Nicolis, G. (1995). *Introduction to Nonlinear Science.* Cambridge: Cambridge University Press.
11. Goldberger, A.L. (1996). Non-linear dynamics for clinicians: Chaos theory, fractals, and complexity at the bedside. *Lancet* 347: 1312–1314; Nicolis, G., Prigogine, Y. (1991). *La complessità. Esplorazioni nei Nuovi Campi della Scienza* Torino: Einaudi; Coffey, D.S. (1998). Self-organization, complexity and chaos: The new biology for medicine. *Nature Medicine* 4: 882–885
12. Harold, F.M. (1986). *The Vital Force: A Study of Bioenergetics.* New York: Freeman and Company.
13. Hahnemann, C.F.S. (1994). *Organon of Medicine.* With explanations by Joseph Reves, edited from the 5th and 6th edition. Homeopress Ltd., Haifa, para. 9.

14. Breithaupt, H. (1989). Biological rhytms and communication. In: *Electromagnetic Bio-Information* (F.A. Popp, ed.). Urban & Schwarzenberg, Munchen, pp. 18–41; Matthews, D.R. (1991). Physiological implications of pulsatile hormone secretion. *Ann. N. Y. Acad. Sci.* 618: 28–37.
15. Berridge, M.J., Morewton, R.B. (1991). Calcium waves and spirals. *Curr. Biol.* 1: 296–297; Strogatz, S.H., Stewart, I. (1994). Oscillatori accoppiati e sincronizzazione biologica. *Le Scienze* 306: 62–68.
16. Cramer, F. (1993). *Chaos and Order: The Complex Structure of Living Systems* Weinheim:.VCH Verlagsgesellschaft.
17. Holland, J.H. (2000). *Emergence: From Chaos to Order Reading.* MA: Addison-Wesley; Solomon, G.F. (1997). Stress, hormones, immunity, the complexity of interwined systems, and the simplicity of humanism. *J. Intensive Care Med.* 12: 219–222; Mainzer, K. (1994). *Thinking in Complexity: The Complex Dynamics of Matter, Mind, and Mankind.* Berlin-Heidelberg: Springer-Verlag; Bellavite, P. (1997). Disease as information disorder. *Advances—Journal of Body-Mind Health* 13: 4–7; Coffey, D.S. (1998). Self-organization, complexity and chaos: The new biology for medicine. *Nature Medicine* 4: 882–885; Kauffman, S.A. (1995). *At Home in the Universe: The Search for Laws of Self-Organization and Complexity.* Oxford: Oxford University Press.
18. Elbert, T., Ray, W.J., Kowalik, Z.J., Skinner, J.E., Graf, K.E., Birbaumer, N. (1994). Chaos and physiology: Deterministic chaos in excitable cell assemblies. *Physiol. Rev.* 74: 1–47.
19. Lorenz, E.N. (1963). Deterministic nonperiodic flow. *J. Atmos. Sci.* 20: 130–141.
20. Lorenz, E.N. (1979). Predictability: Does the flap of a butterfly's wings in Brazil set off a tornado in Texas? Address at the Annual Meeting of the American Association for the Advancement of Science Washington, DC.
21. Shinbrot, T., Grebogi, C., Ott, E., Yorke, J.A. (1993). Using small perturbations to control chaos. *Nature* 363: 411–417; Garfinkel, A., Spano, M.L., Ditto, W.L., Weiss, J.N. (1992). Controlling cardiac chaos. *Science* 257: 1230–1235; Weiss, J.N., Garfinkel, A., Spano, M.L., Ditto, W.L. (1994). Chaos and chaos control in biology. *J.Clin.Invest.* 93: 1355–1360.
22. See Note 18.
23. Callard, R., George, J.T., Stark, J.S. (1999). Cytokines, chaos, and complexity. *Immunity* 11: 507–513.
24. Cotton, P. (1991). Chaos, other nonlinear dynamics research may have answers, applications for clinical medicine. *J. Am. Med. Assoc.* 266: 12–18; West, B.J., Zhang, W., Mackey, H.J. (1994). Chaos, noise and biological data. In: *Fractals in Biology and Medicine (T.F. Nonnemacher, G.A. Losa, and E.R. Weibel, eds.).* Birkhauser Verlag, Basel, pp. 38–54; Bellavite, P., Semizzi, M.L., Lussignoli, S., Andrioli, G., Bartocci, U. (1998). A computer model of the five elements theory of traditional chinese medicine. Complem.Ther.Med. 6: 133–140.
25. Tsong, T.Y., Gross, C.J. (1994). The language of cells: Molecular processing of electric signals by cell membrane. In: *Bioelectrodynamics and Biocommunication* (M.W. Ho, ed.). World Scientific, Singapore, pp. 131–158.
26. Cramer, F. (1993). *Chaos and Order: The Complex Structure of Living Systems* Weinheim:.VCH Verlagsgesellschaft.
27. Nugent, A.M., Onuoha, G.N., McEneaney, D.J., Steele, I.C., Hunter, S.J., Prasanna, K., Campbell, N.P.S., Shaw, C., Buchanan, K.D., Nicholls, D.P. (1994). Variable patterns of atrial natriuretic peptide secretion in man. *Eur. J. Clin. Invest.* 24: 267–274.
28. Goldberger, A.L. (1996). Non-linear dynamics for clinicians: Chaos theory, fractals, and complexity at the bedside. *Lancet* 347: 1312–1314.
29. Freeman, W.J. (1991). The physiology of perception. *Sci. Am.* 264: 34–41.
30. Babloyantz, A., Destexhe, A. (1986). Low dimensional chaos in an instance of epilepsy. *Proc. Natl. Acad. Sci. USA* 83: 3513–3517; Kleiger, R.E., Miller, J.P., Bigger, T., Moss, A.J. (1987). Multicenter post-infarction rg.: Decreased heart rate variability and its

association with increased mortality after acute myocardial infarction. *Am. J. Cardiol.* 59: 256–262.

31. Varela, F.J., Coutinho, A. (1991). Second generation immune networks. *Immunol. Today* 12: 159–166.
32. Bellavite, P. (1997). Disease as information disorder. *Advances—Journal of Body-Mind Health* 13: 4–7; Bellavite, P., Semizzi, M.L., Lussignoli, S., Andrioli, G., Bartocci, U. (1998). A computer model of the five elements theory of traditional chinese medicine. *Complem.Ther.Med.* 6: 133–140; Elbert, T., Ray, W.J., Kowalik, Z.J., Skinner, J.E., Graf, K.E., Birbaumer, N. (1994). Chaos and physiology: Deterministic chaos in excitable cell assemblies. *Physiol. Rev.* 74: 1–47.
33. Kauffman, S.A. (1993). *Origins of Order: Self-Organization and Selection in Evolution.* Oxford: Oxford University Press.
34. Bellavite, P., Semizzi, M.L., Lussignoli, S., Andrioli, G., Bartocci, U. (1998). A computer model of the five elements theory of traditional chinese medicine. *Complem.Ther.Med.* 6: 133–140.
35. Vithoulkas, G. (1980). *The Science of Homeopathy.* New York: Grove Press Inc.; Rubik, B. (1995). Energy medicine and the unifying concept of information. *Altern. Ther. Health Med.* 1: 34–39; Popp, F.A. (1990). Some elements of homoeopathy. *Br. Homeopath. J.* 79: 161–166; Endler, P.C., Schulte, J. (1994). *Ultra High Dilution: Physiology and Physics* Dordrecht: Kluwer Academic Publishers; Poitevin, B. (1993). Les grandes directions de la recherche en homéopathie. In: *Encycl. Med. Nat. Editions Techniques*, Paris: Editions Techniques; Del Giudice, N., Del Giudice, E. (1999). *Omeopatia e Bioenergetica.* Verona.: Cortina International; Eskinazi, D. (1999). Homeopathy re-revisited: Is homeopathy compatible with biomedical observations? *Arch. Intern. Med.* 159: 1981–1987; Schulte, J. (1999). Effects of potentization in aqueous solutions. *Brit. Hom. J.* 88: 155–160; Endler, P.C., Schulte, J. (1997). *Homoopathie und Bioresonanztherapie: Physiologiche und Physikalische Voraussetzungen Grundlagenforchung.* Wien.: Medizinverlag Maudrich.
36. Ho, M.W., Popp, F.A. (1993). Biological organization, coherence, and light emission from living organisms. In: *Thinking About Biology* (W.D. Stein and F.J. Varela, eds.). Addison-Wesley Publ. Co., Reading, pp. 183–213.
37. van Rossum, J.M., de Bie, J.E.G.M. (1991). Chaos and illusion. *Trends Pharmacol. Sci.* 12: 379–383.
38. Garner, C., Hock, N. (1991). Chaos theory and homoeopathy. *Berlin J. Res. Hom.* 1: 236–242; Shepperd, J. (1994). Chaos theory: Implications for homeopathy. *J. Am. Inst. Homeopathy* 87: 22–29; Ruiz, G., Torres, J.L., Michel, O., Navarro, R. (1999). Homeopathic effect on heart rate variability. *Br. Homeopath. J.* 88: 106–111; Torres, J.L., Ruiz, G. (1996). Stochastic resonance and the homoeopathic effect. 85: 134–140; Schwartz, G.E., Russek, L.G., Bell, I.R., Riley, D. (2000). Plausibility of homeopathy and conventional chemical therapy: The systemic memory resonance hypothesis. *Med. Hypotheses* 54: 634–637.