Appendix 1

Basic Research and Homeopathy An Update

Introduction

Research in homeopathy may be divided into two main fields: *clinical* research, which tries to answer the great question: does homeopathy work (the problem of efficacy and effectiveness), and *basic* research, which tries to answer the great question of how it works (the problem of the putative action mechanisms). Existing controversy in the discipline of homeopathy strongly suggests a need to conduct further clinical trials and observational studies to establish whether reproducible therapeutic effects of homeopathic treatments can be unequivocally demonstrated.[1] At the same time, there is need for a theory or, at any rate, for viable hypotheses, to provide reasonable explanations for the effects observed.

The controversy surrounding homeopathic treatments stems in part from the seeming lack of a plausible mechanism that explains purported therapeutic effects of ultra-low-dose or high-dilution remedies. In fact, the scientific validity of a therapeutic method does not depend so much on its success rate as on the fact that the clinical results should be consistent with a pathophysiological, biochemical, and pharmacological theory or rationale. As reported by Kleijnen et al. in their seminal review on clinical trials in homeopathy, "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."[2]

It is only through patient, unrestricted, and methodical research conducted on several planes—clinical, laboratory, epidemiological, and physicochemical—that we shall be able to shed light on the many issues that so far remain unsolved. Homeopathic medicine is now incorporating modern medical methods (clinical trials, statistics, computer programs in repertorization, laboratory studies, animal studies). Now several models explaining some of the claims of homeopathy are available.

There are two main theoretical tenets underlying homeopathy: the principle of *similars* and the use of high dilutions called *potencies*. The principle of similars states that patients with particular signs and symptoms can be cured if given a drug that produces similar symptoms in healthy

individuals.[3] As is well known, the homeopathic tradition has developed a method of serial dilution and dynamization (i.e. dilution followed by succussion) that increases the "potency" of the drugs, and this theory has been one of the main obstacles for the acceptance of homeopathy. Moreover, other important tenets of homeopathy are linked to its "holistic" approach to health and disease (Figure 1). These three aspects of homeopathy are strictly related to each other.

Other points upon which traditional homeopathy is based include *Hering's Law* (that during the correct healing process of a given disease, symptoms disappear from the interior to the exterior of the body, from top to bottom, and starting from the last symptoms in the time sequence of appearance), the principle of homeopathic aggravation, the use of single remedies, and the discussed theory of *miasms*.[4]

These great assumptions are being investigated utilizing different experimental systems, making use of human subjects, animals, cells, or chemical solutions. The literature describing such research is rapidly growing.

One could wonder how to choose the experimental system and the level of investigation. In scientific research the level of choice, and as a consequence, the possibility of obtaining relevant results, is dictated by personal interest, technical feasibility, previous experience and, finally, by fortuitous factors.

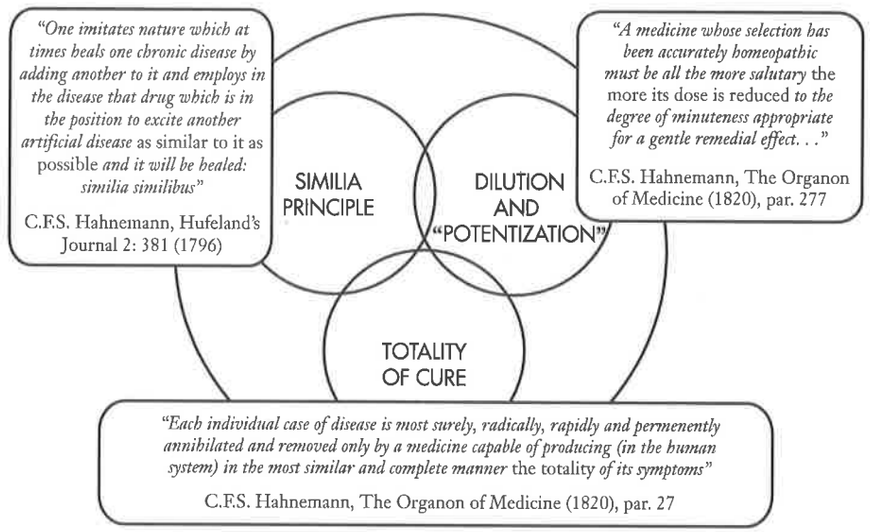

FIGURE 1 The Major Tenets of Homeopathy

"Conventional" basic research in a number of fields of modern biomedical science may be of interest to homeopathic doctors because studies in those fields may provide important evidence for the clarification of one of more of the above-mentioned tenets of homeopathy. In other words, basic research relevant to homeopathy cannot be defined as "homeopathic research," because scientific research has a wider aim than strict medical definition. Homeopathy is a clinical method, a method of cure and of selection of drugs. The study and understanding of its putative action mechanism(s) is neither homeopathic nor allopathic; it is part of the actual development of biomedical science.

In current scientific literature a substantial body of evidence and examples may be extrapolated to topics such as the principle of similarity or the problem of microdose effects, not because homeopathic issues were formulated as a starting hypothesis or discussed as a possible corollary, but because these studies can document and clarify a number of specific aspects of the biochemical regulatory mechanisms that may underlie the observed paradoxical homeopathic phenomena (Figure 2).

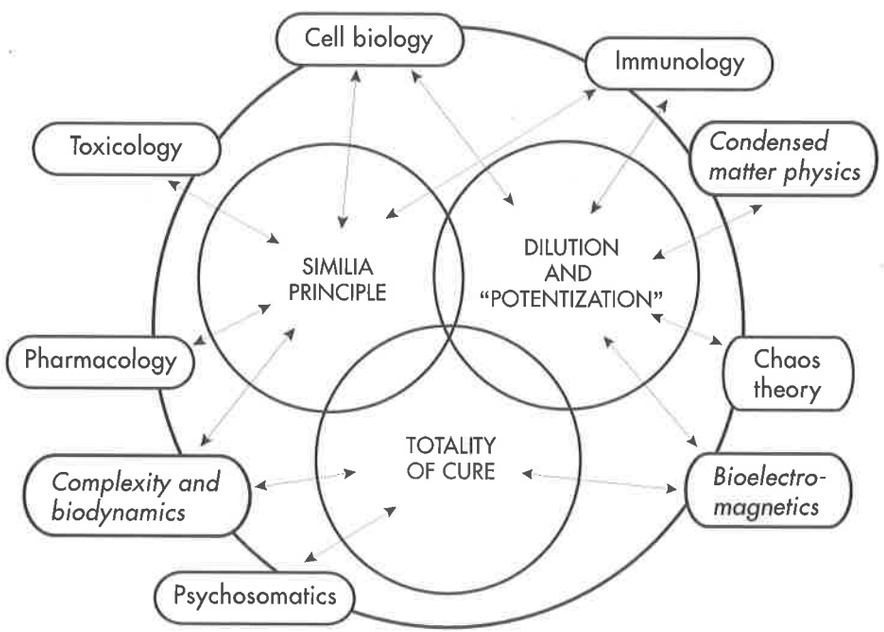

FIGURE 2 Science Fields Involved in Basic Research on Homeopathy

The problems raised by homeopathy are very wide and complex, so no single experiment can clarify everything. We don't have a "theory of everything." Instead, the discipline of homeopathy is being assembled like a puzzle or a mosaic whose pieces are progressively being laid in the right places, and where all the little pieces are important for the realization of the whole image.

It is also important to underline the fact that the scientific puzzle represented by homeopathic claims is now becoming a trigger for the research in these fields. For example, studies sponsored by homeopathic drug companies with the aim of understanding the mechanisms of the *simile* effect, have produced results that have general interest in the fields of immunology, toxicology, and cardiovascular pharmacology.

Before entering into details of some specific experiments, here is a summary of our working hypothesis on the action mechanism of homeopathy. This hypothesis has four main parts:

- Homeopathic medicines may have either chemical (ultra-low-dose) or physical (high-dilution) nature, or both.
- Medicine chosen according to the simile principle may be perceived as harmful by specific biological systems that play a crucial role in the dynamics of the disease.
- Specificity of information may be based on the sensitization of the receiver, on the complexity of the remedy picture, and on the low-dose or high-dilution of the medicine.
- The reaction of the body to the specific "harmful" information may shift the global disequilibrium of the ill person toward a new attractor that is proximal to the health state.

Another important preliminary point is the distinction between very-low dose and high-dilution effects. Both fields fully belong to homeopathy, provided that the medicine is prescribed according to the similia principle and according to a holistic clinical approach. From a scientific standpoint, the mechanism(s) underlying the *similia law* and the effect of microdoses of drugs can be investigated and understood independently of the so-called "high-dilution" or "high-potency" effect.[5] The similia principle is the foundational principle of homeopathy and the *conditio-sine-qua-non* of its definition. Hahnemann originated this system by utilizing low doses of drugs that were available at his time. The principle of *dynamization* or *potentization*, was established in subsequent years, after a number of experimental trials. Moreover, even now the major portion of the market of homeopathic medicines in Europe is represented by medicines containing ponderal doses of active principles.

Here we focus on the similia principle and on the problem of doses, while in Appendix 2 we deal with the problem of the holistic conception of homeopathy.

Similia principle

The similia principle is the basis of homeopathic medicine. It can be formulated as follows:

- Every biologically active substance (drug or remedy) produces characteristic symptoms in healthy bodies which are susceptible to being in some way perturbed by that substance.
- Every sick body expresses a series of characteristic symptoms which are typical of the pathological alteration of that particular subject.
- The healing of a sick body may be obtained by targeted administration of the drug which produces a similar symptom picture in healthy bodies.

The old principle of similarity was formulated as a general "law" on the basis of empirical evidence and analogical reasoning, but this kind of formulation does not allow any progress in the search of the possible mechanism of the alleged therapeutic effects.

Early attempts to empirically investigate the principle of similarity can be traced back to the years around the end of the nineteenth century, when H. Schulz published a series of papers that examined the activity of various kinds of poisons (iodine, bromine, mercuric chloride, arsenious acid, etc.) on yeast, showing that almost all these agents have a slightly stimulatory effect on the yeast metabolism when given in low doses.[6] He then came into contact with the psychiatrist R. Arndt, and together they developed a principle that later became known as the *Arndt-Schulz law*, stating that weak stimuli slightly accelerate vital activity, medium strong stimuli raise it, strong ones suppress it and very strong ones arrest.[7] Similar observations were reported by several other authors in the 1920s, and from their findings one can conclude that the phenomenon of inverse, or biphasic effects of different doses of the same substance was well known before the era of molecular medicine.[8]

Hormesis

The occurrence of dual effects (both stimulatory and inhibitory) caused by the same agent when used at different doses or for different times has been described in various experimental systems and has been often called *hormoligosis*, or *hormesis*.[9] In 1960 Townsend and Luckey surveyed the field

of classic medical pharmacology for examples of hormetic effects and published a wide list of substances known to be capable of causing an inhibition at high concentrations and stimulation at low concentrations.[10] In general, such cases fell into three categories: those involving muscular response, those involving respiration, and those involving transmission of nerve impulses.

Whole-body exposure to low-dose ionizing radiation appears to decrease overall cancer incidence. The data come from at least eight large studies of populations exposed to various forms of radioactive material and from more limited studies of occupational and environmental exposures to plutonium, radium, and radon.[11] Earlier experiments with animals strongly support the protective effect that apparently exists in humans. The combined evidence points to the presence of *no-adverse-effect* thresholds and of hormesis, or beneficial effects, at doses below those thresholds.

In general, these hormetic effects can be documented by a *reverse-u dose-response plot* or even more complex *dose-response curves*. Another possibility is to find a time-course of an intoxication experiment where a high dose causes progressive death of a biological system, a low or intermediate dose causes first a decrease of viability, followed by a recovery and an increase over the basal levels. Rather than being an exception, non-linearity between dose and response are the rule in biological systems. It might even be anticipated that at some doses a response opposite to that seen at high doses could be elicited. Such nonlinearity with dose has multiple implications for numerous aspects of biomedical research on aging and for experimental design.[12]

Despite the substantial development and publication of highly reproducible toxicological data, the concept of hormetic dose-response relationships was never integrated into the mainstream of toxicological thought. Review of the historical foundations of the interpretation of the bioassay and assessment of competitive theories of dose-response relationships lead to the conclusion that multiple factors contributed to the marginalization of hormesis during the middle and subsequent decades of the twentieth century. These factors include the following:

- The close association of hormesis with homeopathy led to the hostility of modern medicine toward homeopathy, thereby creating a guilt-by-association framework and the carryover influence of that hostility in the judgments of medically-based pharmacologists/toxicologists toward hormesis.
- The emphasis of high-dose effects of drugs linked with a lack of appreciation of the significance of the implications of low-dose effects.

- The lack of an evolutionary-based mechanism(s) to account for hormetic effects.[13]

Hormetic effects, which have undoubted importance for the understanding of the similia principle, have been investigated using a number of experimental systems, a few of which are described below.

Laboratory models

The similia principle has been investigated making use of a number of laboratory models. The most important data have been collected using models based on the activation of human basophils, lymphocytes, fibroblasts, renal cells, granulocytes, and vegetable cells.

- The study of basophils has been important mainly for the evidence of high-dilution effects and for the evidence of anti-inflammatory action of histamine.
- Lymphocytes have been used to show the effect of very low doses of interferons and of homeopathic drugs like *Phytolacca*.
- Fibroblasts and renal cells have been used to show the protective effect of very low doses of toxicant on the cellular toxicity exerted by high doses of the same stimulants.
- Granulocytes and platelets have been used for testing homeopathic drugs *in vitro* and for testing the mechanisms of inverse effects from a biological standpoint.

A review of the literature is beyond the scope of this appendix, so we refer here to only a few representative studies and to some of our recent results. More detailed accounts have been reported elsewhere.[14]

In synthesis:

- Dozens of papers report stimulatory or inhibitory effects of homeopathic drugs *in vitro*.
- Most effects on cell systems have been obtained using low doses or very low doses.
- A few groups have reported effects using high dilutions (we mean beyond Avogadro's number), but these effects have not been reproduced by all laboratories.
- The homeopathic similia principle can be found to be operative also at cellular and molecular level.
- Conventional biochemistry, immunology, and cell biology are providing further support for the effect of very low doses.
- Bioelectromagnetics and dynamic systems theory are getting new insights into biological information and communication.

So we are at a good point, but there are also many aspects of the principle that wait for clarification.

An important series of experiments conducted by French groups has shown that very low doses of histamine and of an extract of honeybee (*Apis mellifica*) significantly inhibit basophil degranulation induced by various stimulants.[15] It is worth noting that when delivered to tissue at normal dosages both histamine and honeybee venom have powerful pro-inflammatory irritant properties. Therefore, these experiments clearly illustrate the application of the principle of similarity in an experimental model: a substance that is known to stimulate inflammation at conventional doses is able to inhibit the cell responsible for many phenomena of the acute inflammatory process.

We have developed various models where the functional responses of human blood neutrophils are manipulated *in vitro* in order to express typical inversions of responses on varying the doses of the compounds.

Our first series of experiments in this field was carried out at the beginning of the 1990s. We tested the effects of a large series of compounds at various dilutions on superoxide anion (O_2^-) on blood neutrophils and their adhesion to serum-coated plastic surfaces. This study required a large experimental effort that was sustained in past years by our group and mainly by Dr. Chirumbolo. The data have been published in *The British Homeopathic Journal* in 1993.[16] Superoxide was significantly inhibited by *Manganum phosphoricum* D6 and D8 (33.1±7.35 % and 39.2±5.3 % inhibition of the activity, respectively), and *Magnesium phosphoricum* D6 and D8 (28.3±16.5 % and 30.5±7.4 % inhibition). *Acidum malicum* D4 (53.8±25.8 % stimulation), *Acidum fumaricum* D4 (53.7±33 % stimulation), *Acidum citricum* D3 and D4 (92.0±10.2 % and 9.5±9 % inhibition) stimulated cell metabolism. These effects were highly reproducible in separate experiments. Adhesion function was not modified by any of the tested compounds, suggesting a specificity of the effects on cell metabolism. In the course of the various experiments, *Phosphorus* and *Magnesia phosphorica* often presented inhibitory effects, even at very high dilutions (greater than D15). In five separate experiments done with leukocytes from five different blood donors, we observed the inhibitory effects of certain ultra-high dilution of phosphorus, having done all the right controls to exclude artifacts, but these effects did not always appear at the same dilutions, thus making any statistical assessment of the phenomenon a difficult matter.

In a further series of experiments we found another interesting phenomenon of inversion of effects in the response of human neutrophils to bacterial products. Results showed that pretreatment of neutrophils with low doses of the bacterial peptide fMLP increases their functional respon-

siveness to high doses (a phenomenon that we called *homologous priming*), while the pretreatment with high doses of fMLP decreases their responsiveness to a second treatment with high doses (a typical example of stress-induced receptor down-regulation or *receptor desensitization*).[17] A second finding regarding the granulocyte behavior under specific conditions of stimulation was that high doses of fMLP induce a marked *increase* of cell adhesion to serum-coated plastic surfaces; on the other hand, after pretreatment of neutrophils with the bacterial endotoxin (LPS), in these conditions a low dose of fMLP *inhibits and reverses* the LPS-induced adhesion.[18]

The phenomenon of inversion of effect, according to the precedent state of the cell, was found not only using LPS-treated cells, but also using inflammatory cells, i.e. cells that were harvested from an experimental inflammatory skin exudate.[19] We harvested human neutrophils from inflammatory exudates of skin. We observed that these cells have a tendency to adhere to serum protein-coated culture tubes. Addition of high doses of the peptide fMLP causes a marked *increase* of cell adhesion to serum-coated plastic surfaces; on the other hand, in these conditions a low dose of fMLP *inhibits and reverses* adhesion.

In brief, the chemotactic agent fMLP, which is considered to be an activator of neutrophil adhesion, paradoxically inhibits the same cell response at low doses when used in preactivated cells. We also investigated the mechanism of this phenomenon and found that low doses of fMLP stimulate an increase in cyclic AMP (cAMP) and that addition of cAMP plus theophylline to the LPS-treated neutrophils inhibits the adhesion.[20] Therefore, it is highly conceivable that the phenomenon of inversion of effect in our model system, that is the inhibition of cell adhesion caused by low doses of fMLP, is due to the increase in cAMP triggered by low doses of the cell agonist.

Low potencies of a homeopathic drug extract (*podophyllum*) have specific stimulating effects on the activation of neutrophil metabolism. We made various dilutions of this compound, and then we tested it on our system. Purified *podophyllotoxin* caused a stimulatory (priming effect) on the oxidative metabolism of human neutrophils, the same effect at doses of 0.1–10 µg/ml, while doses higher than 100 µg/ml of *podophyllotoxin* inhibited the respiratory burst, so that pure toxin showed a typical *biphasic* dose-response curve.[21] Low doses have an effect that is similar to the priming effect of TNF-a. Our findings demonstrate that the same toxin causes enhancement of oxidative metabolism at low doses and inhibition at high doses. The interest of this drug comes also from the fact that it is used also by conventional pharmacology at much higher doses as an inhibitor of cell proliferation and appears to be efficacious against condilomata of the skin.

(Low doses are those that are contained in the homeopathic preparation, high doses—the toxic ones—are the doses that are contained in the allopathic preparation.) Homeopathic doses cause a typical hormesis effect. We obtained similar effects using *colchicine*. Both drugs act at the level of cytoskeleton, by inducing a partial disassembly of microtubule network.

Hormesis is a special application of the similia principle at the biological and physiopathological level, but it is important to say that this kind of inverse effect does not represent the *only* explanation of homeopathic effects, which may have further and more complex implications at the level of whole human organism.

As mentioned above, in the biomedical literature there are many reports about specific compounds that exhibit dual effects (positive and negative), according to different doses employed or to different conditions of testing. For example, these paradoxical effects have been reported using prostaglandins, amyloid b-protein, oxygen free radicals, nitric oxide, neuropeptides, cytokines, insulin, acetylcholine, thrombin and many other compounds.[22] We mention these findings in order to draw attention to the complexity of these forms of regulation and to the existence of a subtle balance of opposite actions in all similar homeostatic systems composed by networks of multiple cell types and signals. This complexity is so great that some investigators have found it useful to apply mathematical models to the description of systems such as the immune network. These models have shown that effective regulation of immune disorders can be accomplished with the same antigen or the same lymphocytes that are responsible for the induction of the disease, providing that the doses or the protocols of administration are changed.

Other evidence of inversion of effects on *in vitro* models comes from testing different doses of anti-inflammatory drugs (diclofenac) on human platelets.[23]

Animal models

Several animal models have revealed nonlinear or even opposite responses to the same drugs or to immunoregulatory agents. By plotting the immune response to antigens in laboratory animals versus the doses of antigen used to pretreat the animals we find that the immune response is depressed (state of tolerance) both in animals receiving very low doses and in animals receiving high doses of antigen. Intermediate doses, however, cause a greater response.[24]

Our group at Verona University explored the applications of the similia principle using two models. The first one showed that high dilutions of

histamine are able to modulate the inflammation caused by high doses of histamine in rats.[25] A second rat model was developed by our group, showing that injection of low doses of immune adjuvant (based on killed *Mycobacterium butyricum*) into the peritoneum of rats is capable of preventing and curing the arthritis induced by the injection of high doses of the same adjuvant into the paw.[26] We have also shown that protection by low-dose immune adjuvant is associated with reduction of the pro-inflammatory IL-6 cytokine, with increase of antibodies against Mycobacterium and with increase of circulating nitric oxide derivatives (a possible compensation mechanism).[27]

This is a further example of the induction of tolerance with low doses of antigens, an immunomodulation procedure that has been extensively exploited in recent years for treatment of a number of conditions in humans. We can only mention here a few examples of human therapies, which may be regarded as a special application of the similia principle at the molecular level: the use of bacterial endotoxins as immunostimulants, the treatment of immune disorders with immunoglobulins, of multiple sclerosis with oral myelin, of rheumatoid arthritis with oral collagen, of recurrent bronchitis with bacterial extracts, of allergic diseases with nasal allergens, of cancer with cancer vaccines made with tumor extract or tumor protein components, and of immune disorders with peptides binding to T-cell receptors or to HLA.[28] Most of these therapies are still at the experimental stage, but their existence confirms the increasing acceptance and use of the principle of similarity in modern medicine.

A few years ago researchers at the Harvard Medical School in Boston observed that the autoreactivity of T-cells is managed by the immune system in at least two different ways that are dependent upon the concentration of the antigen they encounter. If they come in contact with high concentrations of a self-antigen, they are deleted (killed), but when given low doses they undergo a special kind of active inhibition (called *bystander suppression*).[29] Other authors have suggested that this type of regulation induced by very low substance concentrations could serve as a model to explain the way in which at least some homeopathic pharmaceuticals mediate their therapeutic effects.[30] The use of sublingual immunotherapy is a typical field where the boundaires of homeopathy (isopathic approach) and of conventional immunology often overlap.[31]

Carrageenan oedema, a classical experimental model commonly used to test activity of anti-inflammatory drugs, was used by our group to evaluate the therapeutic activity of a low-potency mineral complex (MC).[32] The MC was administered in the right plantar surface of albino rats 60 minutes before, simultaneously, and 30 minutes after injection of carrageenan, an irritant that causes a local, transitory increase of fluid volume. The administration of the MC 60 minutes before the injection of carrageenan primed the animal to enhanced inflammatory response to the irritant. The administration of MC contemporarily to carrageenan did not modify the kinetic response and the extent of the oedema, while the administration of the MC 30 min after the induction of the oedema significantly reduced the early phase of the inflammatory reaction. This indicated that the therapeutic action of this MC is not due to conventional anti-inflammatory effect but to activation of endogenous regulatory mechanisms, a phenomenon that may be regarded as a simple application of the similia rule.

Working models of inversion of effects

The investigation of the scientific bases of the principle of similarity, at least as concerns its biological applications, may be facilitated by the formulation of working hypotheses and rational models.

For this purpose we suggest that this principle, in its fundamental meaning, may be traced back to the principle of *inversion of effects*: "biologically active compounds may cause inverse or paradoxical effects on a complex homeostatic system when either the doses of the compound, or the methods of preparation and of administering, or the sensitivity of the target system are changed."

Such an expression of the principle of similarity can be used as an operative definition of an extensive series of biological phenomena ranging from the cellular to the clinical level, the common basis of which may be the versatile adaptability of living systems to external stresses.

This means that a compound (or a treatment) that—according to current knowledge—is considered an inhibitor works as a stimulant, or, the other way around, a stimulant causes inhibitory effects.

Inverse effects that are the biological basis of the homeopathic effect can have various explanations and can be due to various mechanisms, such as the following:

- various receptors (different affinity and different coupling with effectors);
- gating theory (signal transduction);
- heat shock proteins (stress proteins, chaperonins);
- oral tolerance;
- stimulation of counter-regulation at central nervous system level;
- regulation of gene expression;
- regulation of stressed homeostatic networks.

In order to find some explanation of the involved mechanism, we focused on signal transduction and developed a working model that we called *gating theory* , analogous to the role of gating by cyclic AMP in signal transduction pathways.[33] The concept of gating means that in the sequence of signal transmission inside the cell, some signals have a controlling function—gating—that may enhance or block other signals. A gating pathway can positively or negatively regulate information flow through the transmittal pathway and may be activated by intracellular or extracellular signals.

We wanted to find an explanation for inverse effects on adhesion. We tried to find an explanation for how is it possible that a well-known stimulant of adhesion (the bacterial peptide fMLP) becomes an inhibitor of adhesion of LPS-treated cells.

The main assumptions of the model are the following:

- In normal neutrophils, low doses of fMLP induce an increase of cAMP, but not of cell adhesion.
- High doses induce also increase of adhesion.
- The activation mechanism of adhesion by fMLP requires signal transduction pathways different from those necessary for cAMP. In particular, it has been shown that high doses of fMLP induce a rapid and massive activation of phospholipid breakdown, which is a suitable signal for triggering adhesion and oxidative metabolism.
- The increase of cAMP is a signal functionally opposite to that of a high-dose fMLP signal, thus forming a kind of homeostatic balance, a kind of "brake" that prevents a harmful overactivation.

When we use neutrophils that have been previously in contact with LPS, we are in this situation:

- In the absence of fMLP, LPS induces a significant adhesion without increase of cAMP, and low doses of fMLP stimulate cAMP and inhibit adhesion by means of the gating mechanism.
- When high doses of fMLP are used, this inhibition is bypassed and adhesion increases.

Let us draw an analogy using the similia principle. LPS-treated cells represent the "disease" of the leukocyte *in vitro* system, assuming that bacterial LPS mimics the pathological condition. Addition of fMLP represents the therapeutic simile, because this agent causes *similar* pathological effects (adhesion) when tested at high doses in a healthy system (that is on control neutrophils) and therapeutic effects (inhibition of adhesion) when tested in a sick (LPS-treated) system. Clearly this only represents one of a number of possible explanations of apparently paradoxical phenomena that have been described in cell systems.

We were convinced of the general validity of the similia law when we observed some apparently paradoxical phenomena in neutrophils. Our experiments were not designed to investigate homeopathy, but the results drew us to conceive a synthesis between cell biology and homeopathy. Starting from the particular field that we knew so well and directly, we came to consider the general meaning of these phenomena in biological systems.

A different model, based on heat-shock proteins (HSP), has been proposed by the Dutch group of Roeland van Wijk and Fred Wiegant.[34] According to this theory, environmental stress, pathological conditions, and physiological conditions may threaten the organism through different routes (respiration, nutrition, absorption by the skin, etc.). When these toxic compounds or pathological conditions damage cells, one of the most important consequences is damage to cell proteins, which are denatured and may, for example, precipitate in anomalous form inside the cytoplasm. This kind of damage is also called *proteotoxicity*. In response to this damage caused to its proteins, the cells, all the cells, react by utilizing so-called *heat-shock proteins* (HSP). These proteins capture the denatured proteins and neutralize them before they can threaten the functioning of the overall cell metabolism. Therefore, HSP are regarded as the main system protecting the cell from the changes in protein constituents. They are, in other words, a mechanism of self-recovery. Today's knowledge of cell biology gives reasonable insight into the events at cellular level that may be considered analogous to many other processes of self-recovery

In the cytoplasm, HSP exist in a complex relationship with the heat-shock factor (HSF). When protein is utilized for the recovery process, the heat-shock factor is detached and migrates to the nucleus, where it binds to a heat-shock element that in turn activates the transcription of the gene for heat-shock proteins. We have, in a few words, a homeostatic system at the cellular level: the greater the requirement for heat- shock proteins, the greater their production by the cell.

However, a problem arises if this homeostatic system works in a condition of suboptimal response. Several conditions can lead to suboptimal cellular stress response, cell toxicity, and death: excess of toxic load, hormonal and metabolic imbalance that reduces the expression of nuclear HSP or HSF, and damage to cell protein synthetic machinery or energetic supply, with consequent suboptimal HSP synthesis. Such a condition of the cell, in which the reaction to the threat is not optimal, may be considered pathological. The cell could then be considered a "sick system" with the damage insufficiently compensated for.

Here the question is whether compensation can be increased and whether the development of resistance can be stimulated, and if so, how. Van Wijk

suggests that self-recovery will be stimulated with a smaller dose of the substance responsible for disturbing the system in the first place. In practice, this author has shown that self-recovery is defined on the cellular level as supplementing the arsenal of protective proteins, stimulating resistance for the disturbing agent and temporarily stimulating proliferation in compensation for cell death.[35]

The model based on the heat-shock proteins is important because it helps us to understand how a toxic compound could become therapeutically useful and protective. In brief, a low dose of a toxic agent would act according to two possible mechanisms:

- increase of available HSP by favouring its detachment from HSF;
- increase of expression of HSP mRNA.

The gating theory proposed by us and the HSP theory proposed by van Wijk are not alternative but complementary. While the model based on gating at the level of signal transduction helps us to understand the experiments showing the inverse effects of biological compounds which are not toxic; but have regulatory properties through the action on receptors and transduction systems, this model based on HSP attempts to account for results in experiments where the investigators have used homeopathic doses of toxic compounds like arsenic, cadmium, mercury, phosphorus to protect cells,[36] plants,[37] and even laboratory animals[38] from intoxication by high doses of the same or similar toxic compounds. (However, it should be mentioned that this protection model did not work using *Plumbum metallicum* as potential protective agent against plumbum intoxication in rats.[39])

It is worth note once again that these results are not *an explanation for homeopathy*, but a demonstration of *how the homeopathic concept of similia principle can be explained in a precise experimental model.* Every model has a value, which necessarily is limited to the phenomena that it tries to explain. Probably in our experimental model of inversion of effects the production of HSP is not involved, because the effect is very rapid and does not require protein synthesis.

The following is a summary of the experimental evidence for the similia principle/inversion of effects:

- Stimulation or protection by low doses of toxic compounds (typical hormesis effect) on cell and animal models.
- Inhibition of specific cellular activities by low doses of stimulating compounds.
- Inhibition or protection of autoimmunity by low doses of antigen;
- paradoxical effects of drugs.
- Therapeutic effects of low doses/high dilutions of toxic compounds in humans (classical homeopathy).

Based on these findings, we can expect *inversion of effects* to be obtained in three fundamental ways:

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

A relevant point of the model concerns the concept of *sensitivity* of the system under treatment. Modern cell biology and immunology have shown that the sensitivity of biological systems (and of individuals) to a given treatment may vary considerably according to a number of factors ranging from genetic predisposition to environmental conditioning, and to previous experience.

The problem of dilution/dynamization

Homeopathic medicines are used in very-low doses, in ultra-low doses, or even in high dilutions-dynamizations. The concept of dose is obviously related to the receiver system, so that it is impossible to establish narrow limits between these three ranges of doses. We suggest that the term *very-low-dose* may be used when the dose is low but in the range of action of natural substances on biological systems (i.e. just above the threshold dose that can be described by dose-effects plots); the term *ultra-low- dose* may be used when the dose is in the molecular range (concentrations of active principle above Avogadro's constant, that is, about 10^{-23} mol/Liter), but below the dose that is considered to be active by consensus based on most experimental systems. Evidence of the action of ultra-low doses (in the range 10^{-10} to 10^{-20} mol/liter) of substances on specific cellular and subcellular systems can be retrieved from scientific literature independently of studies on homeopathic drugs.[40]

Biological systems can achieve a high degree of sensitivity to external messages, so that they can be regulated by a few molecules. (A typical ex-

ample is the response to pheromones.) The action of ultra-low-doses poses a challenge to biology because it can be seen as an "anomalous effect" to claims for the existence of amplification mechanisms of biological information. In any case, the possible action mechanism of homeopathic drugs in the potency range between first decimal (D) or centesimal (C) dilutions and 20D or 10C dilutions can be found inside the chemical-molecular paradigm. Of course, this view does not exclude the possibility that the effect of succussion during the process of homeopathic serial dilutions changes the physico-chemical structure of the medicine so that its interaction with living matter is based on further and more efficient information transfer mechanisms (for example the transfer of electric charges or protons through hydrogen bonds of water chains).[41]

As for the purported action of high-dilution/high-potency homeopathic drugs, here the problem of finding a rational and consistent explanation is much more difficult, essentially due to lack of consistent experimental data reproduced in different laboratories. There are a number of experiments showing stimulatory or inhibitory effects of highly diluted compounds[42] and showing the existence of peculiar physico-chemical states in water that are compatible with the hypothesis that structure (and information) can be stored in liquid water.[43] Moreover, these data are in agreement with quantum electrodynamic theories (QED).[44]

The basic idea of this reconsideration of QED in condensed matter, liquid and solid, is that *macroscopical* assemblies of identical *microscopic* systems, below a certain temperature (the critical temperature), and above a particular density (the critical density), behave in a way completely different from an ensemble of microscopic objects kept together by short range, electrostatic forces, as is now universally believed. The fundamental new aspect of the theory is that the interactions among the microscopical systems (atoms and molecules) are not restricted to the *nearest neighbors*, but extend over typical domains, of the size of the wavelength of the electromagnetic field that vibrates at the common frequency of the matter systems. Such *coherence domains* represent the fundamental building blocks of condensed matter, inside which matter (atoms, molecules, electrons, and nuclei) oscillates in tune (technically: *in phase*) with a macroscopic (classical) electromagnetic field, much in the same way as it happens in a familiar laser, with the fundamental difference that the coherent e.m. radiation is now trapped permanently inside the CDs, its function being to hold the system together against the wild assaults of the thermal fluctuations.[45]

In spite of these experimental and theoretical advancements, the results demonstrating the high-dilution/high-potency effect are not so consistent and reproducible as they should be for general acceptation by the scientific community.[46] The present state of knowledge does not allow definite conclusions in favor of or against the existence of specific physical states of highly diluted homeopathic remedy. Skeptics are not convinced by the available evidence. On the other hand, people with a more open-minded position are reinforced in their belief that "anomalous states" of water and "condensed matter physics" are giving to high-dilution/high potency homeopathy an increased credibility.[47] Our belief is that the phenomena described in many "high-dilution" experiments do really exist, but they are difficult to reproduce because the experiments are markedly affected by minimal technical differences and conditions, including the skill of the operator, the type of blood donors, the season and the day of the experiment, perhaps atmospheric pressure, the electromagnetic "pollution" of the laboratory, trace contaminants of the water solutions used to make the dilutions, the time left between a dilution and the subsequent, and other factors.

Homeopathy used with ultra-diluted drugs is thus a tentative approach to the bioenergetic regulation of the human body, utilizing a physical-biochemical interface due to the extreme sensitivity of biological systems to this type of regulation. The potential strength of the method consists in the fact that it attempts to achieve the maximum possible degree of *specificity* of the exogenous regulatory intervention. How can the maximum specificity of information be achieved, if we know so little about such bioenergetic systems? The answer is in the main principle of homeopathic tradition, the *law of similars*. This fundamental principle, based, as it is, essentially on the observation of *effects* (i.e. on comparison of the effects of the drug with those of the disease), is in a certain sense independent of any knowledge of the mechanism that causes the effects and thus also applies to the metamolecular level, once we have admitted the existence of the latter. Further details regarding this important point of homeopathic theory can be found in earlier sections of this book.

Homeopathy and homeostasis

The question now arises of whether the similia principle, which seems scientifically proven and which is a general law of nature, can be applied also to traditional homeopathic medicine, a method which is based essentially on *symptom similarity* as detected in human subjects.

We have not a definite answer to this point, but we would like to suggest a possible way to find the answer. Our hypothesis is based on the consideration of the complexity of physiological homeostasis.

Each living system is endowed with homeostatic systems that allow the action of a harmful agent to be counterbalanced by internal adaptation mechanisms. The concept of *homeostasis* in its essential make-up consists of a *set of anatomical, biochemical, and functional elements designed to maintain physiological variables within minimum and maximum oscillation limits.* Homeostatic systems are present at each level of biological organization: at *cell level,* (e.g. membrane transport systems, enzyme induction, heat-shock proteins, cyclic nucleotides), at *organ level* (e.g. regulation of blood flow, of numbers in cell populations, of structure and morphology), at *apparatus level* (e.g. regulation of blood pressure, thermoregulation, bowel function, sexual cycle, etc.), and at *superior function level* (e.g. mental and emotional functions, personality, character, decisions and frustrations, etc.).

All these properties may be summed up with the sophisticated *action-reaction* principle that governs homeostasis: the body (and the cell) does not simply behave passively but also actively. Reversible deviations from this norm tend to set into operation certain phenomena whose chief characteristic is reestablishment of the norm.

The concept of homeostasis, first introduced by the physiologist W.B. Cannon in 1929,[48] refers to all those activities that cooperate in the integration of all the mechanisms that allow a physiological variable to be maintained in the proper variation interval. Hundreds of years before, the principle of action and reaction was outlined by Hahnemann: "Every agent that acts upon the vitality, every medicine, deranges more or less the vital force, and causes a certain alteration in the health of the individual for a longer or a shorter period. This is termed primary action. To its action our vital force endeavors to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of secondary action or counteraction."[49]

A typical sequence of physiological mechanisms that maintain the homeostasis in the immune and endocrine system involves hypothalamic centers that are connected with higher centers and send messages to the hypophysis (corticotropin releasing hormone, CRH) and to the locus ceruleus, the main center controlling the sympathetic nervous system. The hypophysis, in turn, produces several hormones, one of which is ACTH (adrenocorticotropic hormone) that stimulates the adrenal glands to release corticosteroids. Steroid hormones have several functions. One is the suppression of production of ACTH and of CRH, thus representing a negative feedback loop with respect to its own production. Another activity of steroids is the suppression of lymphocyte proliferation and of inflammatory reactions. A similar feedback scheme is found also in the sympathetic nervous system, a system that may be activated by the hypothalamic centers and by higher centers, leading to the final production of noradrenaline, which, in turn, has inhibitory properties on white cells.

Another important pathway connects the peripheral white cells with the central nervous system, through the release of a number of specific proteins, like Interleukin-1, Interleukin-6, Tumor necrosis factor, and so on. These molecules not only serve the purpose of activating the immune system but have specific receptors at several levels of the central nervous system. They can activate the hypothalamus and thus cause various reactions including the production of CRH. This is only a small part of the neuroendocrine control of the so-called general stress response. The important thing is to focus on the multiple feedback regulatory loops that occur in these homeostatic systems.

We have said that the homeostasis is a network of molecular and nonmolecular information that is exchanged between nerve centers and endocrine glands, but one can also envisage a homeostatic network inside each tissue and each system. We have represented here a small piece of this puzzle, the piece that is being investigated regarding the relationships between the various types of inflammatory cells and immune cells.

Without entering into detail, there is a large series of both stimulatory and inhibitory cytokines that reciprocally influence the behavior of macrophages, lymphocytes, and granulocytes. It is well known that inside these cell populations there are either stimulatory (helper) cells or inhibitory (suppressor) cells. Recently, inside the helper populations, two distinct subpopulations have been described, TH1, which is involved in cellular immunity, and TH2, which is involved in humoral immunity and tends to suppress cellular immunity. These regulatory networks can be found also inside the cells, as we have discussed earlier (in connection with HSP/HSF, receptor dynamics).

Regulation of stressed homeostatic networks

Let's see what happens when a stressful stimulus is applied to such a system. To limit ourselves to the essential points, we can see that a psychosocial stress activates the neuroendocrine pathway "from above" the so-called HPA axis (hypophysis-pituitary-adrenal) and the sympathetic system, which ultimately can lead to increase of corticosteroids and decrease of inflammatory reactions. The psychosocial stress can also lead to suppression of immunity and increased susceptibility to infections. A chemical or biological stress, for example, the presence of bacterial toxins inside the tissue or inside an organ, may first activate the peripheral inflammatory reactions, and then these cells will produce cytokines, which in turn reach the

central nervous system where they cause several effects, including the activation of the "response to stress" in a similar way.

In a complex system of homeostasis, using this model, it can be shown that the symptoms are produced by the increased activity of the homeostatic pathways that have been recruited by the disease process. Symptoms (headache, fever, cough, nasal discharge, skin spots, decrease of libido, anxiety, and other psychological changes) are the expression of the reaction of homeostatic systems. Even pain may be regarded as the expression of the local stimulation of sensitive nervous receptors by prostaglandins and neuropeptides, and of the complex elaboration of the signal at the central level

We have developed a model that attempts to put in more simple and general terms the structure of a typical homeostatic system and, most important, to relate it to the similia principle. This model allows prediction of the behavior of any homeostatic system. Exogenous or endogenous stressors may modify the activity of one or several systems, leading to a biphasic respónse.

First, there is an increased response, during which we observe that the systems that have been recruited are primed. We have represented the priming of the system as an increase of receptors that appear on the surface of the system itself. One example is a cell like a lymphocyte (that is an essential part of immune homeostasis). When a lymphocyte is stimulated by a cytokine or by a specific antigen, it is primed, or activated, and expresses on its plasma membrane an increased number of receptors for many compounds. (Of course, we are now describing a model, a general model of homeostatic systems, so we use the term "receptor" not as a precise molecular structure, but as an abstract term that means sensitivity of the system to regulation by some external signal.)

Examples of *priming* include the following:

- Cellular models (e.g. leukocytes): increase of *sensitivity* or of *response* to a second stimulus after the challenge with a first stimulus.
- Tissues (e.g. bronchial reactivity in asthmatics).
- Organs (e.g. liver induction of detoxifying enzymes after ingestion of alcohol or drugs, heart hypertrophy after repeated exercise).
- General systems (e.g. immune hypersensitivity after challenge with antigens).

The second phase of the homeostatic reaction to a stressful stimulus is represented by a decrease of response, mainly due to *desensitization*. The desensitization of a system to a specific stimulant is initially selective for that stimulant (*homologous*) while the system may remain responsive and usually is *primed* to different stimulants acting through different receptors.

The appreciation of this general biologic mechanism—confirmed in a number of experiments in our and other laboratories—is very important in order to understand the physiopathological basis of the similia principle.[50]

During the phase of desensitization the system undergoes pathologic adaptation and chronicization. As a consequence, the disease continues to be maintained due to the lack of response of one or more homeostatic systems. The important thing to note is that maintaining the disorder can continue even if the original stressor is no longer present. This may occur because the network of many interrelated homeostatic systems can be set in several different schemes of behavior (patterns), that correspond, roughly speaking, to different *dynamic attractors*. The system can be set to an attractor, "learn" and consolidate this "pathological behavior," and thus be unable to find the "right way" to change towards the healthy, primary behavior.

A typical example of loss of homeostasis is the resistance to steroids and the central resistance to cytokines that may be an important pathogenetic mechanism in conditions like AIDS,[51] allergy,[52] melancholic depression,[53] and aging.[54] AIDS patients with hypercortisolism and clinical features of peripheral resistance to glucocorticoids are characterized by abnormal glucocorticoid receptors in their lymphocytes, and resistance to glucocorticoids implies a complex change in immune-endocrine function, which may be important in the course of immunodeficiency syndrome.

Any "loss of communication" in the homeostatic systems is deleterious (meaning truly pathological) because the disorder of the homeostatic systems is maintained and can not recover spontaneously.

Possible mechanisms of the loss of communication in the homeostatic systems include the following:

- Homologous desensitization.
- Loss/inactivation of signal molecules.
- Auto-antibodies to receptors.
- Inhibitory effects of bacterial toxins.
- Chemical toxins: food, pollution, drugs, smoking.
- Endogenous toxins: free radicals, complement factors, etc. ("homotoxins").
- Connective tissue sclerosis.
- Deposition and "impregnation": cholesterol, amyloid, glycogen.
- Anomalous gene expression: oncogene activation and anti-oncogene deletion, viruses.

Coming back to our general model, the question is how to stimulate the recovery of the homeostatic communication when there is a block of normal response to the stressor and the system falls under erroneous adaptation. Here it is important to point out that desensitization of a system to a

specific stimulant is initially selective (that is specific) for that stimulant (homologous), while the system may remain responsive and usually is primed to different stimulants acting through different receptors. Most biological systems (cells, tissues, organs,, and so on) have a number of different receptor sensitivities that are capable of triggering the same effector and regulating responses. The extent of expression of these sensitivities varies over time and according to the "experience" of the system itself. So it should be possible, at least in theory, to bypass homologous desensitization and utilize other sensitivities of the same system to push the homeostatic balance in the right direction.

From this perspective, the most suitable regulatory drug is the drug that is capable of directing the recovery of homeostatic equilibrium through *the stimulation of primed sensitivities* of the regulatory systems. This drug may be a specific molecule if we know precisely the level of the disorder, i.e. the specific receptor that should be stimulated (for example, a cytokine or a neurotrasmitter receptor). However, when the loss of homeostasis is due to multiple factors and to subtle causes, it is often hard to identify the specific biochemical blocks and the specific molecules to be supplied. If we deal with blood glucose concentration, we need only few hormones to keep it under control, but if we deal with complex changes and adaptation mechanisms occurring at different levels of homeostatic networks, it is very difficult to find the right stimulant or the right inhibitor for the involved systems. Moreover, the effect of a specific drug on the whole organism cannot always be predicted on the basis of the knowledge of simple models, because the same drug may sometimes have opposite effects according to the dose and the sensitivity of the patient, or may have a number of adverse effects. (These are typical problems of cytokines.)

"The more we learn, the less certain we are."[55]. In a few words: often the doctor doesn't know what to put in this syringe, doesn't know which type of cytokine could be useful to his particular patient in that particular moment of the evolution of its disease.

When the pathogenesis of the disease involves a fine balance of different regulatory systems at the neuroendocrine level, it is very difficult to apply a single or a few drugs using a molecular approach. This is the case in the most widespread diseases in Western countries. For example, it has been recently shown that the tendency to suppress emotional distress ("type-D personality") is a significant predictor of long-term mortality in patients with coronary heart disease, independently of established biomedical risk factors.[56] That means that among people with the same cholesterol levels, the same blood pressure and the same smoking habits, those with a certain personality succumb to heart disease and death much more frequently.

These types of symptoms are not reducible to a single neurobiological mechanism. We know little about the biochemical differences between the different personality profiles, but we know that these have a great impact on the health of the individuals. How can we apply a correct regulatory intervention in these conditions?

Of course, one could say that personality can be cured using psychotherapy, but though this is easy to say, it is extremely difficult to perform. Most doctors don't know how to perform psychotherapy, and most patients that would probably benefit from psychotherapy don't want to go to a psychotherapist. Therefore, the search for a medical approach is necessary, and we should try to find a medicine that helps to restore homeostasis at these levels also.

All who are familiar with homeopathy know how much importance this paradigm gives to psychological factors in the pathogenesis of the disease and in the effect of the drugs.

The logic of the simile

We now are in a position to appreciate the "logic" of the similia principle proposed by homeopathy: if we don't know the primed receptors and their stimulants, there is still the possibility of reactivating the "blocked" systems by administering the specific stimulant identified through symptom similarity. The correct drug is the drug that in a healthy (and sensitive) subject stimulates some systems of the body-mind complex, thus causing the appearance of symptoms qualitatively similar to those of natural disease. In other words: we can identify the right medicine for the right systems in the diseased body-mind complex by checking the effects caused in a healthy system. If the drug produces the same or similar symptoms that are produced by the disease, that drug is the correct one, because its specific target systems are the same systems that are involved (blocked, but still exhibiting some primed sensitivities) in the disease.

After having tried several drugs on healthy systems, and after having identified a specific drug that causes that typical pattern of that specific drug, it is time to introduce into the system information that helps to recover the correct homeostasis. If the original stressing factor is no longer present, the system will find the way to reenter the previous attractor, and thus, to become finally and definitely healthy.

The two approaches—reductionistic and holistic—are not in contrast: mainstream pharmacology uses a *structural analogy*, identified as the right molecule for the right receptor or for the right target system (if they are known). Classical homeopathy uses a *functional analogy*. We call it func-

tional because it is identified by the function that it carries out with regard to the target system, the function being to cause the appearance of symptoms in healthy people and the reinduction of homeostasis in sick people. Functional analogy can be used also if we don't know the details of receptors and of a target system into the complex network of homeostatic systems.

Mainstream pharmacology is more precise when the exact mechanism of the disease is known, and specific remedies can be administered. Homeopathy is more effective when the complexity and subtle dynamics of disease are considered. Through the latter approach, the careful analysis of symptoms and the application of the similia principle may bypass our ignorance of the details of complex biological homeostatic networks. Symptom similarity is a possible guide at ultra-complex levels, dealing with the intimate nature of information disorders in each subject. In a few words, homeopathy may be regarded as the best exploitation of homeostasis rules in complex systems.

Moreover, the classical homeopathic approach, based on symptom analysis, has a number of advantages:

- Symptoms are the expression of the typical reaction of individual homeostatic systems.
- Symptom appearance is very sensitive and is often the earliest manifestation of a homeostatic disorder.
- Symptoms language is psychosomatic and complex by nature. It can be used also as a symbolic language of the body.
- Symptoms analysis is very cheap.

So we can say that this complexity makes working with symptoms advantageous—because it allows the understanding of the true language of complex systems—but, at the same time, is the reason for the difficulty of homeopathy to be accepted as a practical therapeutic method. It is difficult because symptom language is complex.

Hahnemann wrote: "The great, the sole therapeutic law of nature: cure by symptom similarity!" and found an empirical method of cure that was considered by many doctors and patients to be highly effective.[57] Two hundred years later, using a scientific standpoint we could say that the claim of this method as the "sole therapeutic law" is not true. As a matter of fact many years after Hahnemann, the scientific, experimental medicine discovered many effective drugs that have been employed with success to diseases according to different "therapeutic laws" (for example, antibiotics, anti-cancer drugs, insulin, anti-inflammatory agents). These new discoveries led to the erroneous belief that homeopathy was no longer

necessary and without scientific bases. However, only a few decades after the discovery of these new drugs, we have found that they do not cure all diseases and have serious adverse effects. At this point the claim that symptom similarity could be a good therapeutical approach to many diseases shows its potential usefulness in a new, more rational light. From this standpoint, homeopathy may again be at the frontier of medical science.

References to Appendix 1

1. Cucherat, M, Haugh, M.C., Gooch, M, Boissel, J.P. (2000). Evidence of clinical efficacy of homeopathy: A meta-analysis of clinical trials. HMRAG. Homeopathic Medicines Research Advisory Group. *Eur. J Clin. Pharmacol.* 56: 27–33.
2. Kleijnen, J, Knipschild, P, ter Riet, G. (1991). Clinical trials of homeopathy. *BMJ* 302: 316–323.
3. Hahnemann, C.F.S. (1796). Essay on a new principle for ascertaining the curative powers of drugs, and some examinations of the previous principles. *Hufeland's Journal* 2: 391–439.
4. Guajardo G, Bellavite P, Wynn S, Searcy R, Fernandez R, Kayne S. (1999). Homeopathic terminology: A consensus quest. *Br. Homeopath. J.* 88: 135–141.
5. Bellavite, P, Andrioli, G, Lussignoli, S, Signorini, A, Ortolani, R, Conforti, A. (1997). Scientific reappraisal of the "Principle of Similarity." *Med. Hypoth.* 49: 203–212.
6. Schulz, H. (1877). Uber die Theorie der Arzneimittelwirkung. *Virchow's Archiv.* 108: 423–434; Schulz, H. (1888). Uber Hefegifte. *Arch. Fuer Physiol.* 42: 517–541.
7. Martius, F. (1923). Das Arndt-Schulz Grundgesetz. *Muench. Med. Wschr.* 70: 1005–1006.
8. Boyd, L.J. (1936). *A Study of the Simile in Medicine.* Philadelphia: Boericke and Tafel; Oberbaum, M, Cambar, J. (1994). Hormesis: dose-dependent reverse effects of low and very low doses. In: *Ultra High Dilution* (P.C. Endler and J. Schulte, eds.). Kluwer Acad. Publ., Dordrecht, pp. 5–18.
9. Calabrese, E.J. (1999). Evidence that hormesis represents an "overcompensation" response to a disruption in homeostasis. *Ecotoxicol. Environ. Saf.* 42: 135–137 ; Olivieri, G. (1999). Adaptive response and its relationship to hormesis and low dose cancer risk estimation. *Hum. Exp. Toxicol.* 18: 440–442; Calabrese, E.J., Baldwin, L.A. (1998). Hormesis as a biological hypothesis. *Environ. Health Perspect.* 106 Suppl. 1: 357–362 ; Renn, O. (1998). Implications of the hormesis hypothesis for risk perception and communication. *Hum. Exp. Toxicol.* 17: 431–438; Stebbing, A.R.D. (1998). A theory for growth hormesis. *Mutat. Res.* 403: 249–258; Luckey, T.D. (1997). Radiation hormesis. In: *Signals and Images* (M Bastide, ed.). Kluwer, Dordrecht, pp. 31–39; Calabrese, E.J., Baldwin, L,A. (1993). Possible examples of chemical hormesis in a previously published study. *J. Appl. Toxicol.* 13: 169–172; Von Zglinicki, T., Edwall, C., Ostlund, E., Lind, B., Nordberg, M., Ringertz, N.R., Wroblewski, J. (1992). Very low cadmium concentrations stimulate DNA synthesis cell growth. *J. Cell Sci.* 103: 1073–1081; Macklis, R.M., Beresford, B. (1991). Radiation hormesis. *J Nucl. Med.* 32: 350–359; Sagan, L.A. (1989). On radiation, paradigms and hormesis. *Science* 245: 574; Stebbing, A.R.D. (1982). Hormesis: the stimulation of growth by low levels of inhibitors. *The Science of Total Environment* 22: 213–234.
10. Townsend, J.F., Luckey, T.D. (1960). Hormoligosis in pharmacology. *J. Am. Med. Ass.* 173: 44–48.
11. Luckey, T.D. (1999). Nurture with ionizing radiation: a provocative hypothesis. *Nutr. Cancer* 34: 1–11.
12. Johnson, T.E., Brunsgaard, H. (1998). Implications of hormesis for biomedical aging research. *Hum.Exp.Toxicol.* 17: 263–265.
13. Calabrese, E.J., Baldwin, L.A. (2000). The marginalization of hormesis. *Hum. Exp. Toxicol.* 19: 32–40.
14. Linde, K., Jonas, W.B., Melchart, D., Worku, F., Wagner, H., Eitel, F. (1994). Critical review and meta-analysis of serial agitated dilutions in experimental toxicology. *Hum. Exp. Toxicol.* 13: 481–492; Bastide, M. (1994). Immunological examples on ultra high dilution research. In: *Ultra High Dilution* (P.C. Endler and J. Schulte, eds.). Kluwer Acad. Publ., Dordrecht, pp. 27–33; Bellavite, P., Lussignoli, S., Semizzi, M.L., Ortolani, R., Signorini, A. (1997). The similia principle: From cellular models to regulation of homeostasis. *Brit. Hom. J.* 86: 73–85; Eskinazi, D. (1999). Homeopathy re-revisited: Is homeopathy compatible with biomedical observations? *Arch. Intern. Med.* 159: 1981–1987.
15. Davenas, E., Poitevin, B., Benveniste, J. (1987). Effect on mouse peritoneal macrophages of orally administered very high dilutions of silica. *Eur. J. Pharmacol.* 135: 313–319 ; Davenas, E., Beauvais, F., Amara, J., Robinson, M., Miadonna, A., Tedeschi, A., Pomeranz, B., Fortner, P., Belon, P., Sainte-Laudy, J., Poitevin, B., Benveniste, J. (1988). Human basophil degranulation triggered by very dilute antiserum against IgE. *Nature* 333: 816–818; Poitevin, B., Aubin, M., Benveniste, J. (1985). Effect d'Apis Mellifica sur la degranulation des basophiles humains in vitro. *Homéopathie Franc.* 73: 193–198 ; Belon, P., Cumps, J., Ennis, M., Mannaioni, PF., Sainte-Laudy, J., Roberfroid, M., Wiegant, F.A.C. (1999). Inhibition of human basophil degranulation by successive histamine dilutions: Results of a European multi-centre trial. *Inflamm. Res.* 48: S17–S18; Sainte-Laudy, J., Belon, P. (1993). Inhibition of human basophil activation by high dilutions of histamine. *Inflamm. Res.* 38: C245–C247; Sainte-Laudy, J., Belon, P. (1997). Application of flow cytometry to the analysis of the immunosuppressive effect of histamine dilutions on human basophil activation: Effect of cimetidine. *Inflamm. Res.* 46: S27–S28.
16. Chirumbolo, S., Signorini, A., Bianchi, I., Lippi, G., Bellavite, P. (1993). Effects of homeopathic preparations of organic acids and of minerals on the oxidative metabolism of human neutrophils: A controlled trial. *Br. Hom. J.* 82: 227–244.
17. Bellavite, P., Chirumbolo, S., Lippi, G., Guzzo, P., Santonastaso, C. (1993). Homologous priming in chemotactic peptide-stimulated neutrophils. *Cell Biochem. Funct.* 11: 93–100.
18. Bellavite, P., Chirumbolo, S., Lippi, G., Andrioli, G., Bonazzi, L., Ferro, I. (1993). Dual effects of formylpeptides on the adhesion of endotoxin-primed human neutrophils. *Cell Biochem. Funct.* 11: 231–239.
19. Bellavite, P., Carletto, A., Biasi, D., Caramaschi, P., Poli, F., Suttora, F., Bambara, L.M. (1994). Studies of skin-window exudate human neutrophils: complex patterns of adherence to serum-coated surfaces in dependence on FMLP doses. *Inflammation* 18: 575–587.
20. Bellavite, P., Chirumbolo, S., Santonastaso, C., Biasi, D., Lussignoli, S., Andrioli, G. (1997). Dose-dependence of the various functional responses of neutrophils to formylpeptides: Activation, regulation, and inverse effects according to the agonist dose and cell condition. In: *Signals and Images* (M. Bastide, ed.). Kluwer Acad. Publ., Dordrecht, pp. 111–119.
21. Chirumbolo, S., Conforti, A., Lussignoli, S., Metelmann, H., Bellavite, P. (1997). Effects of Podophyllum peltatum compounds in various preparation's dilutions on human neutrophil functions in vitro. *Brit. Hom. J.* 86: 16–26.
22. See note 5.
23. Andrioli, G., Lussignoli, S., Gaino, S., Benoni, G., Bellavite, P. (1997). Study on paradoxical effects of NSAIDs on platelet activation. *Inflammation* 21: 519–30.
24. Weiner, H.L., Friedman, H., Miller, A., Khoury, S.J., Al Sabbagh, A., Santos, L., Sayegh, M., Nussemblatt, R.B., Trentham, D.E., Hafler, D.A. (1994). Oral tolerance: Immunologic mechanisms and treatment of animal and human organ-specific autoimmune diseases by oral administration of autoantigens. *Annu. Rev. Immunol.* 12: 809–837; Weiner, H.L. (1997). Oral tolerance: Immune mechanisms and treatment of autoimmune diseases. *Immunol. Today* 7: 336–343.
25. Conforti, A., Signorini, A., Bellavite, P. (1993). Effects of high dilutions of histamin and other natural compounds on acute inflammation in rats. In: *Omeomed92* (C. Bornoroni, ed.). Editrice Compositori, Bologna, pp. 163–169.
26. Conforti, A., Lussignoli, S., Bertani, S., Verlato, G., Ortolani, R., Bellavite, P., Andrighetto, G. (1997). Specific and long-lasting suppression of rat adjuvant arthritis by low-dose Mycobacterium butyricum. *Eur. J. Pharmacol.* 324: 241–247; Conforti, A., Bertani, S., Lussignoli, S., Bellavite, P. (1998). Pharmakodynamik und komplexe Systeme. In: *Biologische Mediczin in der Orthopedie/Traumatologie, Rheumatologie* (H. Hess,

ed.). Baden Baden: Aurelia Verlag, Baden Baden, pp. 39–52; Conforti, A., Lussignoli, S., Bertani, S., Ortolani, R., Brendolan, A., Cestari, T., Andrighetto, G., Bellavite, P. (1998). Suppression of adjuvant arthritis in rats by intraperitoneal Mycobacterium butyricum. *J. Chemother.* 10: 169–172.

27. Conforti, A., Lussignoli, S., Bertani, S., Ortolani, R., Cuzzolin, L., Benoni, G., Bellavite, P. (2001). Cytokine and nitric oxide levels in a rat model of immunologic protection from adjuvant-induced arthritis. *Int. J. Immunopathol. Pharmacol.* 14:153.
28. See Note 5.
29. See Note 24, Weiner.
30. Heine, H., Schmolz, M. (2000). Immunoregulation via "bystander suppression" needs minute amounts of substances-a basis for homeopathic therapy? *Med. Hypotheses* 54: 392–393.
31. Scadding, G.K., Brostoff, J. (1986). Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. *Clin. Allergy* 16: 483–491; MacDonald, T.T. (1994). Eating your way towards immunosuppression. *Curr. Biol.* 4: 178–181; Trentham, D.E., Dynesius-Trentham, R.A., Orav, E.J., Combitechi, D., Lorenzo, C., Sewell, K.L., Hafler, D.A., Weiner, H.L. (1993). Effects of oral administration of type II collagen on rheumatoid arthritis. *Science* 261: 1727–1730; Taylor, M.A., Reilly, D., Llewellyn-Jones, R.H., McSharry, C., Aitchison, T.C. (2000). Randomised controlled trial of homoeopathy versus placebo in perennial allergic rhinitis with overview of four trial series. *BMJ* 321: 471–476.
32. Bertani, S., Lussignoli, S., Andrioli, G., Bellavite, P., Conforti, A. (1999). Dual effects of a homeopathic mineral complex on carrageenan-induced oedema in rats. *Br. Homeopath. J.* 88: 101–105.
33. Iyengar, R. (1996). Gating by cyclic AMP: Expanded role for an old signaling pathway. *Science* 271: 461–463.
34. Van Wijk, R., Wiegant, F.A.C. (1995). Stimulation of self-recovery by similia principle. Mode of testing in fundamental research. *Br. Homeopath. J.* 84: 131–139; Van Wijk, R., Wiegant, F.A. (1997). The similia principle as a therapeutic strategy: A research program on stimulation of self-defense in disordered mammalian cells. *Altern. Ther. Health Med.* 3: 33–38; Van Wijk, R., Wiegant, F.A.C., Souren, J.E.M., Ovelgonne, J.H., van Aken, J.M., Bol, A.W.J.M. (1997). A molecular basis for understanding the benefits from subharmful doses of toxicants. *Biomed. Ther.* 15: 4–13; Wiegant, F.A.C., Van Wijk, R. (1996). Self-recovery and the similia principle: An experimental model. *Complem. Ther. Med.* 4: 90–97.
35. Ibid.
36. Delbancut, A., Dorfman, P., Cambar, J. (1993). Protective effect of very low concentrations of heavy metals cadmium and cisplatin against cytotoxic doses of these metals on renal tubular cell cultures. *Br. Homeopath. J.* 82: 123–124.
37. Betti, L., Brizzi, M., Nani, D., Peruzzi, M. (1997). Effect of high dilutions of Arsenicum album on wheat seedlings from seed poisoned with the same substance. *Br. Homeopath. J.* 86: 86–89.
38. Bildet, J., Guere, J.M., Saurel, J., Aubin, M., Demerque, D., Quilichini, R. (1975). E'tude de l'action de differentes diluitions de Phosphorus sur l'hepatite toxique du rat. *Ann Homeop. Fr.* 4: 425–432; Palmerini, C.A., Codini, M., Floridi, A., Mattoli, P., Buffetti, S., Di Leginio, E. (1993). The use of Phosphorus 30 CH in the experimental treatment of hepatic fibrosis in rats. In: *Omeomed92* (C. Bornoroni, ed.) Editrice Compositori, Bologna, pp. 219–226; Kundu, S.N., Mitra, K., Bukhsh, A.R. (2000). Efficacy of a potentized homoeopathic drug (Arsenicum-album-30) in reducing cytotoxic effects produced by arsenic trioxide in mice: III. Enzymatic changes and recovery of tissue damage in liver. *Complement Ther. Med.* 8: 76–81; Datta, S., Mallick, P., Bukhsh, A.R. (1999). Efficacy of a potentized homoeopathic drug (Arsenicum Album-30) in reducing genotoxic effects produced by arsenic trioxide in mice: Comparative studies of pre-, post-, and combined pre- and post-oral administration and comparative efficacy of two microdoses. *Complement Ther. Med.* 7: 62–75; Mitra, K., Kundu, S.N., Khuda Bukhsh, A.R. (1999). Efficacy of a potentized homoeopathic drug (Arsenicum Album-30) in reducing toxic effects produced by arsenic trioxide in mice: II. On alterations in body weight, tissue weight and total protein. *Complement Ther. Med.* 7: 24–34; Lapp, C., Wurmser, L., Ney, J. (1955). Mobilization de l'arsenic fixé chez le cobaye sous l'influence des doses infinitesimales d'arseniate. *Thérapie* 10: 625–638 ; Cazin, J.C., Cazin, M., Gaborit, J.L., Chaoui, A., Boiron, J., Belon, P., Cherruault, Y., Papapanayotou, C. (1987). A study of the effect of decimal and centesimal dilutions of Arsenic on the retention and mobilisation of Arsenic in the rat. *Human Toxicology* 6: 315–320; Cazin, J.C., Cazin, M., Chaoui, A., Belon, P. (1991). Influence of several physical factors on the activity of ultra low doses. In: *Ultra Low Doses* (C. Doutremepuich, ed.). Taylor and Francis, London, pp. 69–80.
39. Fisher, P., House, I., Belon, P., Turner, P. (1987). The influence of the homoeopathic remedy plumbum metallicum on the excretion kinetics of lead in rats. *Hum. Toxicol.* 6: 321–324.
40. See Note 30, and Note 14 (Eskinazi).
41. Woutersen, S., Bakker, H.J. (1999). Resonant intermolecular transfer of vibrational energy in liquid water. *Nature* 402: 507–509; Weiss, P. (1999). Vibrations flit along water's fast lane. *Science News* 156: 358.
42. Cristea, A., Nicula, S., Dare, V. (1997). Pharmacodynamic effects of very high dilutions of Belladonna on the isolated rat duodenum. In: *Signals Images* (M. Bastide, ed.). Kluwer, Dordrecht, pp. 161–170; Sainte-Laudy, J., Belon, P., Sainte-Laudy, J., Belon, P. (1996). Analysis of immunosuppressive activity of serial dilutions of histamine on human basophil activation by flow cytometry. Application of flow cytometry to the analysis of the immunosuppressive effect of histamine dilutions on human basophil activation: Effect of cimetidine. *Inflamm. Res.* 45 (S1): 33–34; Youbicier-Simo, B.J., Boudard, F., Mekaouche, M., Bayle, J.D., Bastide, M. (1996). Specific abolition reversal of pituitary-adrenal activity and control of the humoral immunity in bursectomized chickens through highly dilute bursin. *Int. J. Immunopathol. Pharmacol.* 9: 43–51; Schiff, M. (1995). *The Memory of Water: Homeopathy and the Battle of Ideas in the New Science.* London: Thorsons; Bastide, M. (1994). Immunological examples on ultra high dilution research. In: *Ultra High Dilution* (P.C. Endler and J. Schulte, eds.). Kluwer Acad. Publ., Dordrecht, pp. 27–33; Davenas, E., Poitevin, B., Benveniste, J. (1987). Effect on mouse peritoneal macrophages of orally administered very high dilutions of silica. *Eur. J. Pharmacol.* 135: 313–319 ; Davenas, E., Beauvais, F., Amara, J., Robinson, M., Miadonna, A., Tedeschi, A., Pomeranz, B., Fortner, P., Belon, P., Sainte-Laudy, J., Poitevin, B., Benveniste, J. (1988). Human basophil degranulation triggered by very dilute antiserum against IgE. *Nature* 333: 816–818; Betti, L., Brizzi, M., Nani, D., Peruzzi, M. (1997). Effect of high dilutions of Arsenicum album on wheat seedlings from seed poisoned with the same substance. *Br. Homeopath. J.* 86: 86–89; Kundu, S.N., Mitra, K., Bukhsh, A.R. (2000). Efficacy of a potentized homoeopathic drug (Arsenicum-album-30) in reducing cytotoxic effects produced by arsenic trioxide in mice: III. Enzymatic changes and recovery of tissue damage in liver. *Complement Ther. Med.* 8: 76–81.
43. Litime, M.H., Aissa, J., Benveniste, J. (1993). Antigen signaling at high dilution. *FASEB J.* 7: A602; Elia, V., Niccoli, M. (1999). Thermodynamics of extremely diluted aqueous solutions. *Ann. N. Y. Acad. Sci.* 879: 241–248; Schulte, J. (1999). Effects of potentization in aqueous solutions. *Brit. Hom. J.* 88: 155–160; Benveniste, J. (1994). Further biological effects induced by ultra high dilutions: Inhibition by a magnetic field. In: *Ultra High Dilution* (P.C. Endler and J. Schulte, eds.). Kluwer Acad. Publ., Dordrecht, pp. 35–38; Schulte, J. (1994). Conservation of structure in aqueous ultra high dilutions. In *Ultra High Dilutions* (P.C. Endler and J. Schulte, eds.). Kluwer Acad. Publ., Dordrecht, pp. 105–115; Demangeat, J.L., Demangeat, C., Gries, P., Poitevin, B., Constantinesco, A. (1992). Modifications des temps de relaxation RMN a 4 MHz des protons du solvant dans les trés hautes dilutions salines de Silice/Lactose. *J. Med. Nucl. Biophy.* 16 (2): 135–145; Weingartner, O. (1992). *Homoopatische Potenzen.* Berlin-Heidelberg: Springer Verlag; Sachs A.D. (1983). Nuclear magnetic resonance spectroscopy of homoeopathic remedies. *J. Holistic Med.* 5: 172–177; Smith, R.B., Boericke, G,W. (1968). Changes caused by succussion on NMR patterns bioassay of bradykinin triacetate succussions

dilutions. *J. Amer. Inst. Hom.* 61: 197–212; Gregory, J.K., Clary, D.C., Liu, K., Brown, M.G., Saykally, R.J. (1997). The water dipole moment in water clusters. *Science* 275: 814–817; Fesenko, E.E., Gluvstein, A.Y. (1995). Changes in the state of water, induced by radiofrequency electromagnetic fields. *FEBS Lett.* 367: 53–55; Fesenko, E.E., Geletyuk, V.I., Kazachenko, V.N., Chemeris, N.K. (1995). Preliminary microwave irradiation of water solutions changes their channel-modifying activity. *FEBS Lett.* 366: 49–52; Liu, K., Brown, M.G., Carter, C., Saykally, R.J., Gregory, J.K., Clary, D.C. (1996). Characterization of a cage form of the water hexamer. *Nature* 381: 501–503; Widakowich, J. (1997). Microdose therapy: dilution versus potentiation? *Medical Hypotheses* 49: 437–441.

44. Arani, R., Bono, I., Del Giudice, E., Preparata, G. (1995). QED coherence and the thermodynamics of water. *Int. J. Mod. Phys.* B9: 1813–1841; Del Giudice, E., Preparata, G., Vitiello, G. (1988). Water as a free electric dipole laser. *Phys. Rev. Lett.* 61: 1085–1088; Preparata, G. (1995). *Quantum electrodynamic coherence in matter*. Singapore: World Scientific.
45. Preparata G. 1997. Regimi coerenti in Fisica e Biologia. Il problema della forma. Biology Forum. Rivista di Biologia / Biologv Forum 90: 434–436; Del Giudice, E., Preparata, G., Vitiello, G. (1988). Water as a free electric dipole laser. *Phys. Rev. Lett.* 61: 1085–1088.
46. Walach, H., van Asseldonk, T., Bourkas, P., Delinick, A., Ives, G., Karragiannopoulos, C., Van Wassenhoven, M., Witt, C. (1999). Electric measurement of ultra-high dilutions: A blinded controlled experiment. *Brit. Hom. J.* 87: 3–12; Hirst, S.J., Hayes, N.A., Burridge, J., Pearce, F.L., Foreman, J.C. (1993). Human basophil degranulation is not triggered by very dilute antiserum against human IgE. *Nature* 366: 525–527; Maddox, J., Randi, J., Stewart, W.W. (1988). "High-dilution" experiments a delusion. *Nature* 334: 287–290; Walach, H. (2000). Magic of signs: a non-local interpretation of homeopathy. *Br. Homeopath. J* 89: 127–140.
47. Vallance, A.K. (1998). Can biological activity be maintained at ultra-high dilution? An overview of homeopathy, evidence, and Bayesian philosophy. *J. Altern. Complement Med.* 4: 49–76.
48. Cannon, W. (1935). Stresses and strains of homeostasis. *Am. J. Med. Sci.* 189: 1–14.
49. Hahnemann, C.F.S. (1994). Organon of Medicine. With Explanations by Joseph Reves, edited from the 5th and 6th edition. Homeopress Ltd., Haifa, para. 63.
50. Bellavite, P, Andrioli, G, Lussignoli, S, Signorini, A, Ortolani, R, Conforti, A. (1997). Scientific reappraisal of the "Principle of Similarity." *Med. Hypoth.* 49: 203–212; Bellavite, P., Lussignoli, S., Semizzi, M.L., Ortolani, R., Signorini, A. (1997). The similia principle: From cellular models to regulation of homeostasis. *Brit. Hom. J.* 86: 73–85; Eskinazi, D. (1999). Homeopathy re-revisited: Is homeopathy compatible with biomedical observations? *Arch. Intern. Med.* 159: 1981–1987; Bellavite, P., Chirumbolo, S., Lippi, G., Guzzo, P., Santonastaso, C. (1993). Homologous priming in chemotactic peptide-stimulated neutrophils. *Cell Biochem. Funct.* 11: 93–100; Heine, H., Schmolz, M. (2000). Immunoregulation via "bystander suppression" needs minute amounts of substances-a basis for homeopathic therapy? *Med. Hypotheses* 54: 392–393.
51. Norbiato, G., Bevilacqua, M., Vago, T., Baldi, G., Chebat, E., Bertora, P., Moroni, M., Galli, M., Oldenburg, N. (1992). Cortisol resistance in acquired immunodeficiency syndrome. *J. Clin. Endocrinol. Metab.* 74: 608–613.
52. Buske-Kirschbaum, A., Jobst, S., Psych, D., Wustmans, A., Kirschbaum, C., Rauh, W., Hellhammer, D. (1997). Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. *Psychosom.Med.* 59: 419–426.
53. Gold, P.W., Licinio, J., Wong, M., Chrousos, G.P. (1995). Corticotropin releasing hormone in the pathophysiology of melancholic and atypical depression and in the mechanism of action of antidepressand drugs. *Ann N.Y.Acad.Sci.* 771: 716–729.

54. Seeman, T.E., Robbins, R.S. (1994). Aging and hypothalamic-pituitary-adrenal response to challenge in humans. *Endocrine Rev.* 15: 233–266.
55. Cohen, J. (1993). AIDS research: The mood is uncertain. Science 260: 1254–1261.
56. Denollet, J., Sys, S.U., Stroobant, N., Rombouts, H., Gillebert, T.C., Brutsaert, D.L. (1996). Personality as independent predictor of long-term mortality in patients with coronary heart disease. *Lancet* 347: 417–421.
57. Hahnemann, C.F.S. (1994). Organon of Medicine. With Explanations by Joseph Reves, edited from the 5th and 6th edition. Homeopress Ltd., Haifa, para. 50.