THE SIMILIA PRINCIPLE REVISITED

Theoretical bases and experimental evidence for a physio-pathological model based on the reactivation of homeostatic communication

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Andrea Signorini*, Giuseppe Andrioli, Riccardo Ortolani***, Anita Conforti****, Paolo Bellavite*****

* Department for Scientific Reserch of F.I.A.M.O. (Italian Federation of Medical Homeopaths)
** Institute of Chemistry and Clinical Microscopy, Borgo Roma Hospital, Verona
*** Institute of Immunopathology, University of Verona
**** Institute of Farmacology, University of Verona
***** Department of Morphological Biomedical Science, University of Verona

SUMMARY:
Biololgical homeostasis could be seen as a "controlled disequilibrium", capable of governing various cellular tissues and organ functions. Some aspects of cellular behaviour after strong or weak stimulation have been studied in recent years. These raise new prospects of interpreting the complex patterns of response which cells use to maintain homeostasis during different environmental conditions. Changes in cellular sensitivity in response to a prolonged stimulus are connected to changes in receptor density and/or activation. This may influence the change from acute to chronic states. Possibly during the development of the chronic state, a phase shift alters intracellular homeostatic systems, with a loss of biological communication. On the basis of this evidence our model of the "Similia Principle" could be thought of as a "reactivation of stressed biological communication", in which homeopathic remedies serve as resonating regulators of dynamic cellular sensitivity. Starting with this model we put forward the hypothesis that not only could explain the operative level of the similia principle but even permit a theoretical (and also practically based) explanation of some homeopathic phenomena such as "homeopathic aggravation" and the "return of old symptoms". At last we can try to shed light on some ancient homeopathic assertions such as "medicinally induced artificial disease-manifestation", drug "primary and secondary action" and "homeopathic drug provings".

KEYWORDS: homeostasis, stress, leucocytes, receptors, priming, desensitisation, inverse effects, regulatory systems, similar symptoms, homeopathic aggravation, return of symptoms, proving

INTRODUCTION:
The efficacy of homeopathy has been adequately demonstrated (1, 2). Its mechanism of action, however, is quite nebulous. Even in understanding the mechanism of action of high dilutions, we will still be uncertain about the law of similars, which is a general mechanism for both high and low concentrations or dilutions.
Samuel Hahnemann affirmed that the similia principle is the only therapeutic law of nature and in affirming this with such certainty, saw homeopathy as the only possible direct path between two points. Hahnemann also thought it useless to speculate on the inner essence of diseases, which he held to be irrational thinking. But his position was to prefer the practical to the theoretical and to protest against those who wasted time in discussion rather than action. While in those days it was difficult to speculate adequately about the nature of things not yet discovered, it is perhaps more appropriat do so nowadays, in the light of modern knowledge.
To be unaware of the mechanism of action of a therapeutic method is to only have an approximate idea of its function, causing confusion in translating it into practical therapeutics. This frequently would have an adverse

influence on practical application of the technique. An example of such confusion may be seen in the early divisiveness among homeopaths while Hahnemann was yet alive.

Our team of five comprises two university based doctors, one homeopath, one researcher and a pharmacologist. The experiments, from which our hypotheses derive, have been performed in the laboratory of the Institute of Chemistry and Clinical Microscopy of the University of Medicine Verona; from this we derived a physio-pathological model based only on our experimental data. Subsequently we integrated these experimental results and the resulting model with clinical homeopathic experience. This yielded a theoretical model of the Similia Principle based on observations of cellular homeostasis, which lead to biological communication. 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 about symptomatology with an attempt to connect biological changes and the evolution of symptoms must be included in a discussion of the law of similars. Our point of departure is the conviction that every symptom has its own significance and origin, almost invariably connected to biological changes (physical or chemical) in the function and/or structure of protein molecules, cells, tissues and systems. In addressing this connection, based on the first fundamental law of homeopathy, ie the law of similars, we will essentially ignore dilution/dynamization which only modulates and amplifies the signal of the law of similars.
We must first consider Hahnemann's definition of 1796: "One imitates nature which at times cures a chronic disease by means of another supervening disease and if one administers to the disease to be cured, that medicine capable of producing another artificial disease which is as similar as possible, it will be cured: Similia Similibus" (3).

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. Over two hundred years of clinical observations by homeopaths of phenomena such as the initial aggravation of symptoms and the return of old symptoms are relevant to the discussion of our model. Both Hahneamann’s explanation of the law of similars and practitioners’ clinical observations are explained by our biological model and are curiously connected by it.

In attempting to study the biological mechanisms of the law of similars we are inevitably required to discuss homeopathic experimentation or Homeopathic Drug Proving. Accordingly we will present a hypothesis, which is derived from our model of the law of similars, and which attempts to interpret what happens biologically when a homeopathic medicine is administered to a healthy subject.

From our point of view, the Arndt-Schulz law only explains the reversal of effect between high and low doses and in practice only applies to toxic substances (4). What is necessary is a model which is more appropriate to the specificity of symptoms and not only to the reversal of effects. This should apply to all medicinal compounds even if they have no action in material doses. Hence we sought a more general model.

BIOLOGICAL COMMUNICATION: PRIMING AND DOWN-REGULATION

To understand this model one must have a good knowledge of receptor physiology and in particular that the action of a particular agonist on the cell membrane depends as much on cellular sensitivity (number of receptors available to the agonist) as to the intensity of the signal (number of molecules occupying the receptors). Accordingly the intensity of the signal (number and duration of action of agonists) is capable of changing *in an opposite way* the sensibility to the same signal (density of receptors on the cell membrane). This is one of the processes where material doses do not always have the same effect on different individuals nor sometimes even in the same individual during different health conditions.

In fact in stimulating neutrophils with various doses of an agonist (fMLP, 100 or 1000nM) we have demonstrated that doses which are too high and repeated, induce a loss of normal cellular response (5). This was measured by the production of superoxides. This phenomenon is called down-regulation and consists of the diminution in number and/or affinity of the receptors. During down-regulation, which is reversible and rather prolonged in time, the action of the agonist on its receptors is diminished or suppressed.

However, using even a single low dose stimulus (eg 1 nM) the neutrophils do not respond but become hyper-responsive to a second stimulus in higher dose, which acts more intensely than if it had been administered without the preceding lower dose. This pre-activation was defined as "*homologous priming*"

and consists of an increase in the number and or affinity of receptors to the inducing stimulus. In this state of hyper-responsiveness the cell activates intracellular signaling massively and globally as well as those functions which depend on the receptor.

Down-regulation is in general specific to the stimuli used. In contrast *priming is not specific* owing to the sensitisation of receptors to other stimuli (*heterologous priming*). 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 eg: homeopathic aggravation, the return of old symptoms, the origin of symptom modalities, artificial drug-induced disease, the similarity and difference between pathogenesis and treatment.

HOMEOSTATIC STRESS

The model we are using to better study the law of similars is that of classical feedback, where the points of regulation derive from the regulatory system ("RS") and from a variable X which oscillates between the two conditions A-B in a reversible equilibrium (fig.1).
Regulation derives from the molecule or signal *s* (informative) which informs the RS and from the molecule or signal *r* (regulatory) which regulates peripheral effector systems which then act on the the variable equilibrium between A-B.

The model also adresses the fact that the various elements of the system interact with other systems: signals s and r could act on other control and effector systems ("divergence") whereas the regulatory system possesses receptors for other systems and could be influenced by these as well ("convergence"). So, as a rule, homeostatic systems are organised in a net-like fashion comprising many elements.

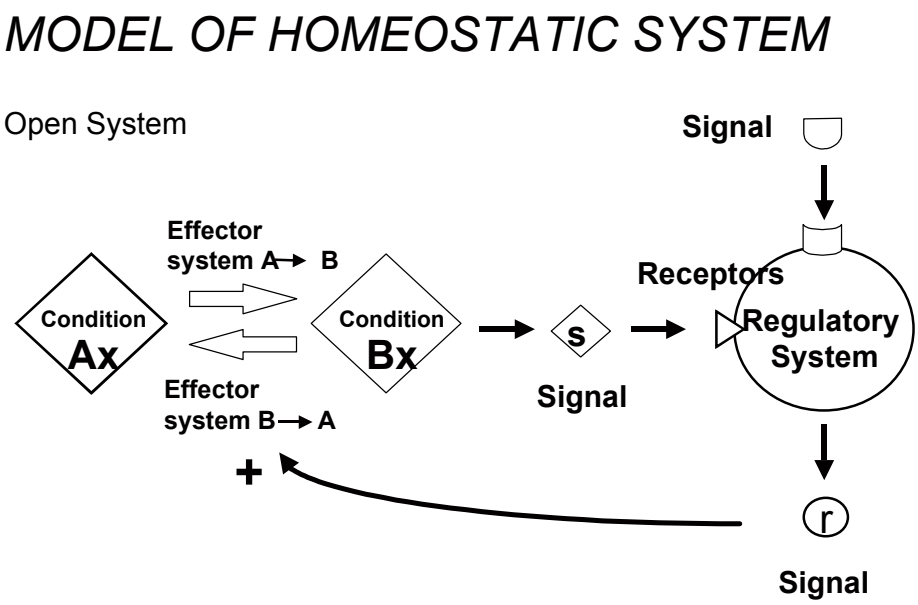

Fig.1: example of homeostatic system. Effector systems regulating the oscillating variable X are controlled by 'regulatory' signals *r* deriving from regulatory system (RS); the RS receives informations on how to regulate effector systems throw 'informative' signal s, the production of which depends on the different conditions of the variable. The RS is not a closed system automatically responding to the signal *s,* but it integrates different signals deriving from other regulatory systems connected in the physiological network (convergence of signals).

When a pathogenic stress alters the equilibrium of the variables, it creates a state of alarm (acute phase) characterised by: a) increase in signals both entering and exciting the RS, and b) increase in receptors, as much towards the increased signals (homologous priming) as towards other different signals not directly

connected to the acute reaction (heterologous priming). This means that when a signal initiates an alarm response, the RS activates all receptive channels (fig. 2).

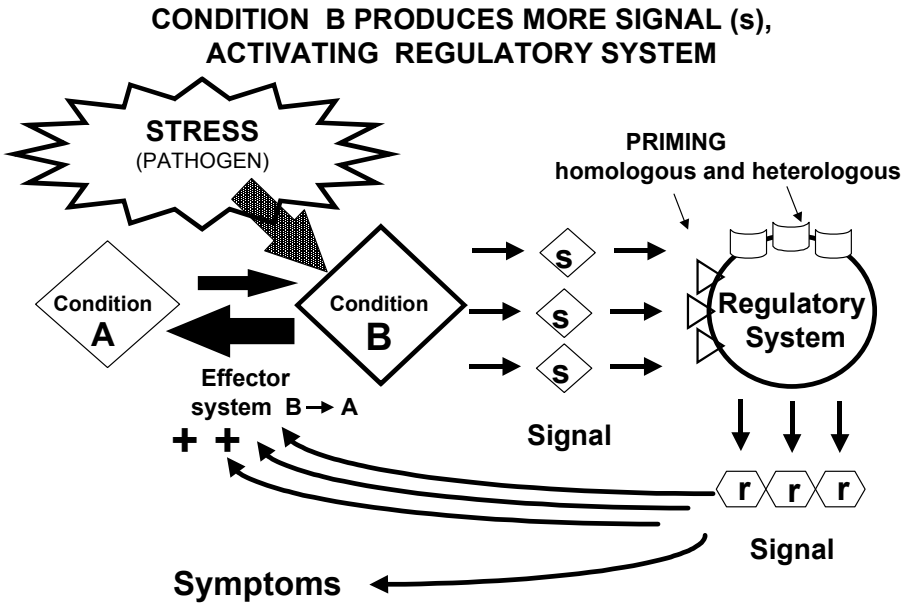

Fig. 2 : the first step of pathologies is acute phase. During this phase the feed-back loop is very activated increasing the number of produced signals and of exposed membrane receptors. The RS becomes hypersensitive not only toward the initial signal (*homologous priming*), but even toward other different signals (*heterologous priming*). In this first pathologic phase one can observe the onset of symptoms, they are the expression of the activation of endogenous systems.

If the stressor vanishes or is removed, the system returns to normal. However the priming remains for a while longer as a form of temporary memory. At the initial stage of the disturbance (which may be more or less "physiological") we see the initiation of symptoms. Symptoms are, in general, connected more to the activation of endogenous systems than the direct effect of the etiological agent. They are the expression of the organism to the disturbance of homeostasis.

If however the stress continues, the organism does not tolerate such a continuing high energy expenditure and prefers not to respond to excessively strong or repeated stimuli.
Down-regulation of the receptors is homologous as initially it is selective for the triggering stimulus, while the system in general remains hypersensitive to other stimuli via other receptors (heterologous priming).
This phase may be considered as the biological representation of the phenomenon of the development of chronicity: the homeostatic dysequilibrium (the true disease) is now self-perpetuated owing to the inadequate response of one or more homeostatic regulatory systems (Fig. 3).

This phenomenon of down-regulation is well recognised in both physiological and pathological states. A physiological example is the pineal gland which produces melatonin in response to a circadian light/dark cycle. It seems that its production depends as much on the input of post-ganglionic sympathetic fibres of the superior cervical ganglion as on the increased or decreased number of the adrenergic pineal receptors (6) with mechanisms of induction typical of priming and reduction which are typical of down-regulation. Pineal adrenergic receptors are modulated not only via circadian rhythms (7) but by age (8), diet and certain types of stress (9,10).

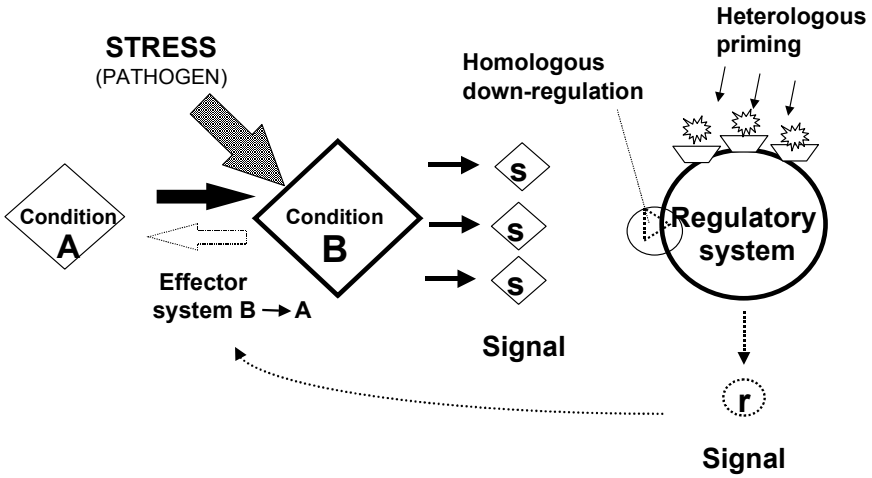

Fig. 3 : the second pathological step is the chronic phase. The homeostatic systems incur a deep change of regulation, they lost the communication with the informational signals s and fail to appropriately react to the disequilibrium of the variable (homologous desensitization). At the same time they manifest hyper-sensitivity to other indipendent signals (heterologous priming)

Another physiological example, but under conditions of stress, is seen in the reduction in platelet adrenergic receptors under conditions of sympathetic activation such as with students doing examinations and marathon runners. A pathological example may be found in the reduction of adrenergic receptors during myocardial infarction (11) and dilational cardiomyopathy (12).

The second phenomenon, perhaps more relevant to our model of the similia principle, is the group of circumstances where the cell determines its heterologous priming. This may allow a possibility of *retrospective intervention* in regard to cellular sensitivity, to permit a reduction in cellular dysequilibrium via alternative regulatory inputs.
In this context it is imperative to mention Hahnemann, who founded his medicinal system on the action/reaction principle. In the 63rd paragraph of the Organon he emphasised that under the primary action of the medication: "Our vital force with its own energy attempts to oppose this action. The action deriving from this has a quality which is supportive of life, it is an automatic response of the vital force and is called 'secondary action' or 'reaction'.....".

SYMPTOMS AND BIOLOGICAL COMMUNICATION

Until now we have discussed changes in cellular reactivity which are well-known and studied in the international literature. Now we need to consider in the light of the above, 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 behaviour" and is incapable of finding "the right path" to original health.

The production of regulatory signal *r* is no longer integrated to the physiological circuit connected to variable A/B, 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 which translate into different and more characteristic symptoms. We may turn matters around at this point and ask if it is diseases or their pathogenic agents which determine these changes in homeostatic systems or is it these latter which

generate the sensibility to disease (or to pathogenic agents). In other words, is it the disease which produces poor homeostasis or vice versa?

Perhaps these events of priming and down-regulation occur dozens of times before the reserves or the organism are exhausted and constitute a true mechanism of pathology ie appearance of disease. When the dysfunction of the regulatory system impinges upon areas of marginal importance, other compensatory regulatory systems come to the rescue. If however the dysfunction strikes in a region of greater importance the alterations in these functions become irreversible.

As long as the organism has supplementary regulatory systems which can contain the advancing disorder, probably only the mildest and most nebulous of symptoms will manifest. While these are of no great worth to conventional medicine, they carry weight in homeopathy. Examples include premenstrual headaches, acidic sweat or sun intolerance. When finally many regulatory systems are in dysequilibrium, 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 (eg fever, pain, vomiting, haemorrhage etc) and b) *Complex or weak symptoms* connected to changes in sensitivity and reactivity of the networks of regulatory systems (Fig. 4).

In this latter group they are more complex, granted that, not being determined by a specific abnormal molecular concentration, are only of minor intensity and accordingly less able to be 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 dysequilibrium.

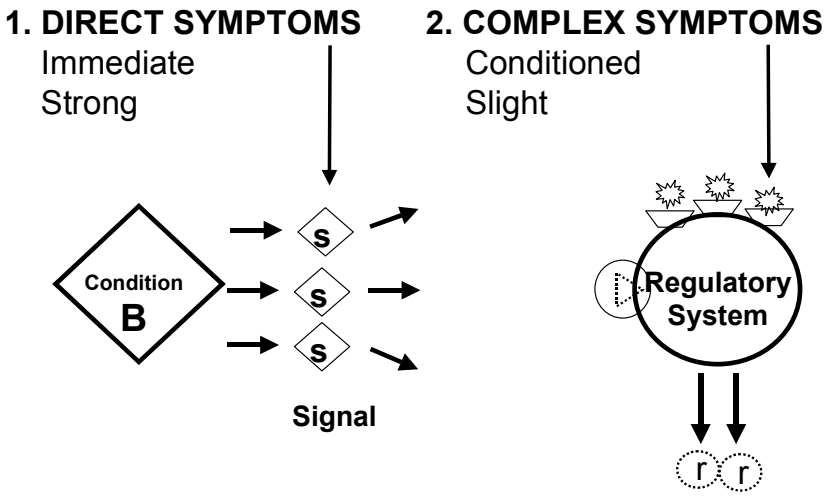

Fig. 4 : two types of symptoms could be observed during the pathological phases. Symptoms due to increased quantity of molecules (ie fever) and symptoms due to change of cell membrane sensitivity.

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. This is exactly what happens in HIV/AIDS, where patients with excessive corticosteroid production develop a gluco-corticoid resistance with obvious clinical worsening resulting from a lack of inflammatory braking (13).

Hence: the loss of communication in homeostatic systems is dangerous (ie truly pathological) because the disorder in the homeostatic system persists and cannot restore itself spontaneously. This is the major

mechanism in the development of the CHRONIC STATE in diseases. If this loss of communication is the true disease, as we think, and responsible for the greater part of chronic diseases, then how to restore it, how to allow homeostasis to recover? Hahnemann replied that there are three ways to treat:

· The first is *to remove the exciting cause*, if possible. Comparing this with our model, this would correspond to the elimination of the pathogenic stressor. Hahnemann called this way 'royal', but probably it is truly so only before the adaptation state, during acute phase.
· The second involves *antidoting specific symptoms* (palliative treatment). In our model this corresponds to molecular modulation of informative signals or of the ligand-receptor interaction. This treatment does not change the chronic 'disequilibrium' of regulatory systems, but only corrects some of its worst consequences.
· The third is the way of the *law of similars*. This, in our model corresponds to the modulation of the processes of stimuli integration into the regulatory system. In this way the treatment tries to reactivate the blocked regulatory systems using the same language (physico-chemical signals and receptors) the same points (target zones) and the same direction of the simptoms.

Even current neuro-pharmacology is seeking different strategies to classical competitive agonist/antagonist interaction. This has resulted from the abundant clinical observations of tolerance and dependence, both physical and psychological (14). The choice of the path of the law of similars is the most appropriate. In our model it corresponds to the study of receptor sensitivity and of their precise and subtle regulation. At this point we must ask ourselves several questions:
A)Does the physician know the hypersensitive receptors in the new situation which are responsible for the symptoms (*knowing the disease*)?
B) Does the physician know and possess the molecules appropriate for their regulation (*knowing the medicine*)?
C) Does the physician know the priority they have during the curative treatment in every specific type of disease (*choice of medicine corresponding to the case*)?
D) Does the physician know the correct doses (*knowing the dose*)?
Recalling paragraph three of the Organon, we note that Hahnemann's statements about the necessary level of knowledge of the physician to allow one to prescribe correctly would give the perfect answer to these questions.

Thinking in molecular-biochemical terms we must recognise the great difficulties in understanding ligand-receptor interactions, the majority of which, as yet, have been little studied in detail. Moreover we do not understand or even know all the hormones and neurotransmitters necessary for the organism, and we know even less of their receptors. In the last decades the body of scientific knowledge has greatly increased, but the current prevaling attitude in conventional therapeutics does not permit to use of the law of similars.

THE LAW OF SIMILARS AND HOMEOSTATIC REACTIVATION

It is clear that we must seek a different solution, one that is more practical and accessible. Hahnemann's solution, **the totality of the symptoms**, seems to address itself to this model for the following reasons:
a) We may readilly accept 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 receptores) present within the organism.

b) Moreover if we knew the correct heirarchy 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 utilisation of such medications would address or modulate the microscopic dysequilibrium 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 developing 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 which are regulated in a complex fashion and by agonist/antagonist couplings which differ from one tissue to another, as with subtypes of receptors to adrenaline, histamine and serotonin. We may see at the microscopic level the possible result of using such a drug. If it is true, as follows from our hypothesis, that **homeopathic modalities** *are more connected to receptor sensitivity and homeostatic networks than to the action of molecular signals*, the use and hierarchy of such symptoms would correspond to an indirect study of such sensitivity. And the difference between studying cell sensitivity or molecular actions on the cell is quite

different, because the last is very similar to the action of an external drug, the first 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 cellular regulatory systems would force the cell to recover its 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 (Fig. 5).

It is possible that, during the pathological phase, an excessive stress on homologous receptors has made the the system "sick", causing a loss of communication and a heterologous hypersensitivity. In contrast, during the therapeutic phase we may stress the hyperactive receptor, rendering it "artificially sick" in order to "heal" the communication which was lost. In this case the homeopathic remedy would act as a *stronger stimulus* on the same receptors to which the disease has given a state of hyper-stimulation. To continue to stress this way with material doses, following our model, would have the consequence of inducing another desensitisation and loss of other communications. If however, we use diluted remedies this risk is probably very low and the result could be only an attenuation of the hypersensitivity. 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.

HYPOTHETICAL ACTION OF HOMEOPATHIC MEDICINE

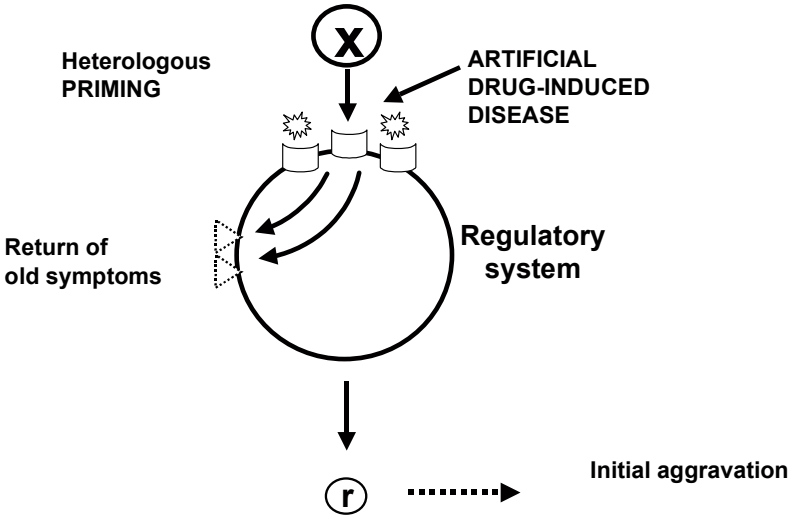

Fig. 5 : in this figure some phenomenon of the peculiar homeopathic healing response are demonstrated. See the text for comments.

A loss of communication ought not to produce many symptoms, and could remain silent and hidden. However the hypersensitivity related to this ought to produce obvious and clear symptoms. In acting on this last-mentioned channel pathway with sufficient force to overcome the dysequilibrium, would this signify that this sensitivity became "pathological"? In reducing it to a less active state would we see "unblocking" and reactivation of the associated sensitivity which had been silent?

Should this question be given a positive answer it would certainly confirm our model as stated above and align our hypothesis with clinical homeopathy.

So, if our remedy acts on the stimulated receptors, the first effect to be expected is an increase in symptoms (*initial aggravation*) until it led 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 in over-activated for a long time (years), the reactivation of its receptors will, of its nature, lead to a reappearance of symptoms which disappeared when their function was lost.

THE LAW OF SIMILARS

What then is the action of the homeopathic medicine during experimentation or proving? All substances used in provings on the healthy produce physio-pathological changes corresponding to their vector of action which translate into peculiar symptoms. These effects are a consequence of specific action on their corresponding cell and tissue sensitivity connected to the direction of their action (primary action). If our hypothesis is solid based we may accept the results of some experiments demonstrating that intercellular communication over long distances is regulated by forces of a physical nature (15, 16). So even high dilutions would have the capacity to stimulate cellular receptor sensitivity. Let us see where the law of similars is situated according to this model (fig.6).

A) During disease, as a result of excessive molecular signalling, certain symptoms develop. In a subsequent phase desensitisation (down-regulation) occurs accompanied by heterologous hyperactivity. This determines a certain functional dysequilibrium, 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 or to cell sensitivity disequilibrium) . These 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, precisely because of their weakness, are more sensitive to modulation and to present themselves as a consequence of a particular modality.

B) During toxicological experimentation the direct action of drugs in material doses on structures receiving them (receptors) determines the symptoms. These are specific for each drug. If the doses used during homeopathic experimentation (**proving**) are quite attenuated, it is possible that the symptoms that arise, (17, 18, 19) may be due to an unknown physico-chemical phenomenon. This would be determined only by *an increase in sensitivity of the same receptors*. The resulting onset of a particular symptoms will derive from the modulation or integration of homeostatic networks for the action of low dosages on cellular targets. This is not only a hypothesis because the priming effect of low dosage substances is well known and we have a few experiments at very low dosage which confirmed that.

Coming back to pathological state, during a disease, symptoms similar to those of 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 in their totality, either from hyper-sensitivity 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 law 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 physico-chemical and 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. Adapting this model to these phenomena has not placed any strain on the pre-existing model which we had previously elaborated to explain apparently paradoxical (non-linear) biological phenomena observed with material doses of agonists on leucocytes and platelets.
The limitations of this work are certainly not homeopathic dilutions themselves, as homeopathy would not exist if the law of similars only applied to high dilutions. At a cursory reading, this mechanistic reasoning might seem to be remote from the complexity, richness and totality of symptoms imbued in the organism as a whole. However a cell, a human being or the planet Earth may be considered to be a small section of something larger (human being, global society or the Universe respectively) and too insignificant to be of

account in understanding the complex dynamics moving in the structures of which they are part. However the contrary is true as well.

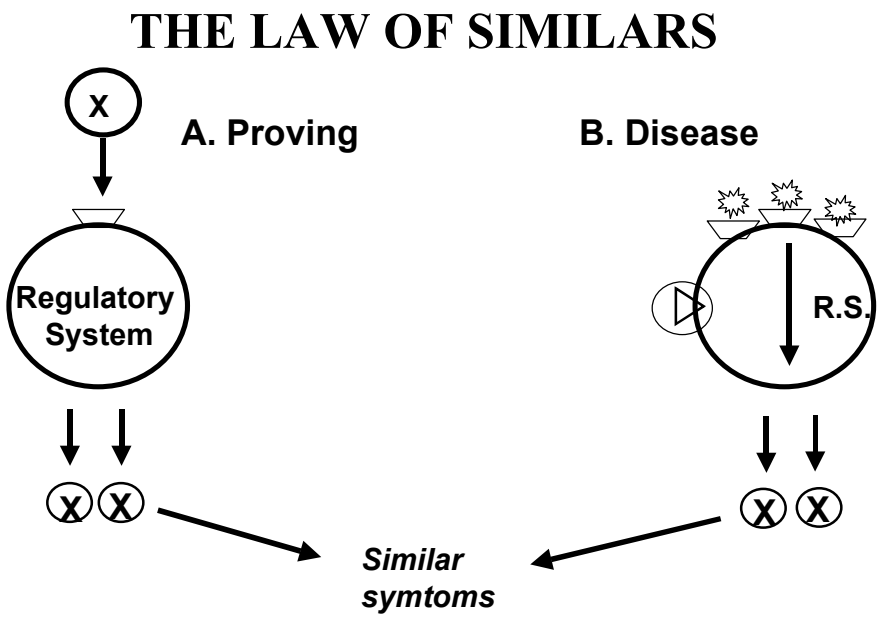

Fig. 6 : biological hypothesis of the law of similars. See the text for comments.

A cell, a person or the planet may also be considered, each according to their scale of size, as living systems, concealing within themselves smaller entities, also bearing qualities typical of life, where chaos and complexity act marvelously, diffusely and unpredictably and are rules of the phenomena called life.

Rather, a limit of our model could be the fact that we do not know if it is true for all symptom groupings or is limited to those of the excitatory remedies, as it is more probable following our observations. Two more consistent objections to our model may consist in the lack of experimental prooves regarding the possibility that a) homeopathic dilution interact with membrane receptors and that b) this action may invert the microscopic dynamic disequilibrium of homeostatic systems. With regard to the first objection we refer to other specific works where this argument is based on solid data (1). As yet we lack objective in regard to the second possible objection. In proposing our tentative hypotheses we take heart from Claude Bernard's statements, that only by daring to make and to hopefully verify such hypotheses may human knowledge progress.

BIBLIOGRAPHY

1. Bellavite, P. e Signorini, A. (1995) Homeopathy: a Frontier in Medical Science. Controlled Studies and Theoretical Foundations. North Atlantic Books, P.O. Box 12327, Berkeley, CA 94712, USA. (Ed. Italiana: Fondamenti Teorici e Sperimentali della Medicina Omeopatica. Nuova Ipsa Editore, Palermo).
2. Kleijnen J., Knipschild P., ter Riet G. (1991) Clinical trials of homeopathy. *Brit. Med. J.* 302 :316
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
4. Shulz A. (1888) Uber Hefegifte. *Arch Fuer Physiol.* 42: 517-541
5. Bellavite, P., Chirumbolo, S., Lippi, G., Guzzo, P. and Santonastaso, C. (1993) Homologous priming in chemotactic peptide stimulated neutrophils. *Cell Biochem. Funct*. 11: 93-100.
6. Gonzalez-Brito A. et al. (1988) Darkness-induced changed in noradrenergic input determine the 24 hour variation in beta-adrenergic receptor density in the rat pineal gland: in vivo physiological and pharmacological evidence. *Life Sci*. 43(8):707-14.
7. Kafka MS. et al. (1981) Circadians and seasonal rythms in alpha- and beta-adrenergic receptors in the rat brain. *Brain Res.* 207(2):409-19.

8. Henden T. et al. (1992) Age-associated reduction in pineal bet-adrenergic receptor density is prevented by life-long food restriction in rats. *Biol. Signals* 1(1):34-9
9. Yocca FD et al. (1984) Effect of immobilization stress on rat pineal beta-adrenergic receptor-mediated function. *J. Neurochem*. 42(5):1427-32.
10. Bellavia SL and Gallara RV. (1998) Modification of the beta- and alpha2-adrenergic sensitivity of rat submandibular glands by environmental stimuli and stress. *Arch. Oral Biol.* 43(12):933-9.
11. Anthonio RL. et al. (2000) Beta-adrenoceptor density in chronic infarcted myocardium : a subtype specific decrease of beta1-adrenoceptor density. *Int J Cardiol* 15;72(2):137-41.
12. Merlet P. et al: (1992) Myocardial beta-adrenergic desensitization and neuronal norepinephrine uptake function in idiopathic dilated cardiomyopathy. *J Cardiovascular Pharmacol* 19(1):10-6
13. Norbiato et al. (1992) Cortisol Resistance in Acquired Immunodeficiency Syndrome. J. Clin. Endocrinol Metab. 74 : 608-13
14. Scapagnini U. (1989) Psiconeuroendocrinoimmunologia. Liviana Ed. Padova.
15. Tsong T.Y. (1989) Deciphering the language of cells. *Trends Biochem.Sci.* 14: 89
16. Liu D.S. et al. (1990) Activation of Na+ and K+ pumping modes of (Na,K)-ATPase by an oscillating electric field. *J. Biol. Chem.* 265: 7260
17. Signorini A., Castellini M., Del Carlo A. (1999) La scheda raccolta dati e metodologia di un proving omeopatico. *Il Medico Omeopata* March 1999, 10: 33-5
18. Signorini A. (1999) Il Proving Medicinale Omeopatico nelle Scuole di Omeopatia. Atti del 1° Congresso F.I.A.M.O, Roma, Ottobre 1999
19. Signorini A., Buffo A., Castellini M., Falco M., Penna S. (2000). Arsenicum bromatum: a three-years proving. Atti del 2° Congresso F.I.A.M.O. Roma, 6-8 Ottobre 2000 (in press)