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PHYSIOPATHOLOGICAL MODELS OF THE SIMILIA PRINCIPLE

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INTRODUCTION

The similia principle, or principle of similarity, is the basis of homeopathic medicine. It can be formulated as follows: *a*) 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; *b*) every sick body expresses a series of characteristic symptoms which are typical of the pathological alteration of that particular subject; *c*) 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 attempt to construct a plausible model of the mechanism(s) of the similia principle and therefore of "homeopathic" effects like the inversion of the effect according to the doses or to the sensitivity of the body is the main aim of the present work. In synthesis, we suggest that the reappraisal of the similia principle in modern terms can be formulated as follows: *"Similia similibus curentur"="Biologically active compounds may cause inverse or paradoxical effects on a complex system when either the doses of the compound and/or the sensitivity of the system are changed."* We try to expound this concept both at cellular level and at the level of the whole living system and to advance a series of hypotheses based on experimental findings. Scientific knowledge proceeds from experience to hypothesis and from hypothesis to experimental tests and homeopathy may follow the same pathway for its progress.

Possible models explaining inverse and/or paradoxical effects at a cellular level are: a) gating theory, based on signal transduction; b) presence various receptors, having different affinity and different coupling with effector systems; c) heat-shock proteins, also called stress proteins, or chaperonins; d) induction of detoxification enzymes (gene expression and enzyme activation).

We have developed a model explaining inverse effects (=similia principle) at a cellular level. We have seen a large series of experimental evidence obtained in cellular system, pointing to the existence of a general principle of inversion of effects and non-linear dose-response relationships.

PRIMING AND INVERSE EFFECTS

In this section we report experimental data pointing to the changes of responses and of sensitivity of cellular systems under various conditions of stress, caused by the addition of various compounds for which neutrophils have specific receptors. Although related to certain particular experimental models, our studies help to understand some general phenomena of the complex regulation of biological systems and anticipate some concepts that we will utilize for the construction of a model of action of homeopathic remedies.

Investigations on multiple responses of neutrophils to bacterial products (2) showed that direct addition to the cells in colture of a high dose (e.g. 100 nM or 1000 nM) of the bacterial peptide fMLP induces a rapid response in terms of superoxide production; however, if the same high dose is repeated after 10 minutes, the cells do not respond any more. They have lost the sensitivity to this stimulant, a phenomenon called *desensitization*. Moreover, a low dose of fMLP (e.g. 1 nM) do not cause any superoxide response of neutrophils. However, if, after ten minutes, a higher dose (e.g. 100 nM) is added to the cell incubation mixture, a great response is obtained (as increase of superoxide production), much greater than the response of control cells, i.e. of the cells treated with high dose but which have not received the low-dose priming. This experiment showed that a low dose sensitized the cells to a high dose, made them more responsive, and this is exactly what we mean by the word *priming* and more precisely *homologous priming* because it is due to the same substance.

Homologous priming is associated with an increase of membrane receptors for fMLP and other stimulants; desensitization is associated with a marked decrease of membrane receptors for fMLP. However, it should be pointed out that the desensitization is specific for the stimulant used: after treatment with either low or high doses of fMLP the cells are still normally responsive or even primed to other stimulants like opsonized yeast, lectins, or phorbol esters. On the other hand, after pre-treatment with either low or high doses of bacterial endotoxin (*E. coli* lipopolysaccharide, LPS), the cells are primed to enhanced response to fMLP. These important physiopathological modifications of cell receptors ares called *heterologous priming*. We and others described it both on cell colture and on *"in vivo"* inflammatory models (3). These data are summarized in table 1.

Table 1. Regulation of the superoxide production in human neutrophils.

Cell pre-treatment	Stimulant used	Effect of pre-treatment *
Low dose fMLP	High dose fMLP	↑ (=homologous priming)
High dose fMLP	High dose fMLP	↓ (=homologous desensitization)
Low/high dose LPS	High dose fMLP	↑ (=heterologous priming)
Low/high dose fMLP	High dose phorbol esters	↑ (= heterologous priming)

* The effect of the in vitro pretreatment was evaluated by comparing the superoxide production by neutrophils stimulated after the indicated pre-treatment with the production by neutrophils stimulated without pretreatment.

Table 2. Dose-dependence of various functional responses of human neutrophils to bacterial peptides (fMLP). The results are summarized from the papers cited in parentheses.

Tested function	Low doses fMLP (1 to 10 nmoles/l)	High doses fMLP (100 to 10,000 nmoles/l)
Superoxide production (2)	–(priming only)	↑
Adhesion (normal cells) (4)	–(=no effect)	↑
Adhesion (LPS-primed cells) (4)	↓	↑
Adhesion (*ex vivo*-primed cells) (5)	↓	↑
fMLP receptor expression (2)	↑	↓
Cytosolic [Ca++] (2)	↑	↑
Cytosolic [cAMP] (4)	↑	↑

We then observed inverse effects of different doses of fMLP on the adhesion of human neutrophils (4). We studied the adhesion responses to fMLP of neutrophils which were treated with bacterial endotoxin (lipopolysaccharide, LPS). By investigating the dose-response relationships of the adhesion response in these cells, we have observed an unexpected phenomenon: a) in control cells doses of fMLP higher than 50 nM stimulate the adhesion, as expected and as described in the literature; b) using the cells treated with LPS we noted that priming augments cell adhesion to serum-coated culture wells in the absence of further stimulation; c) high fMLP doses (> 50 nM) increase the adhesion and are additive to the spontaneous adhesion induced by priming; d) in LPS-treated cells, addition of low, substimulatory doses of fMLP (0.5 to 5 nM) inhibits and reverses the spontaneous adhesion. Therefore, 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 primed cells.

In other tests, using other stimulants like phorbol esters or concanavalin A instead of fMLP, we didn't find any inversion of effects on changing the doses (4, 5). Therefore, the phenomenon seems to have a definite stimulus-specificity, probably because different stimuli use at least partially different signal transduction pathways inside the cell.

The reversal of adhesion by low doses of fMLP was detectable not only in LPS-treated cells, but also in tumor necrosis factor (TNF-α)-treated cells and in inflammatory cells, i.e. in neutrophils that were harvested from a skin experimental inflammatory exudate (5). This indicates that it is not a laboratory artefact but plays a physiological role in the leukocyte kinetics and the distribution of the cells inside the body.

We also found that the low doses of fMLP induce a rapid actin polymerization at the level of cytoskeleton and cause a variety of intracellular modifications at the level of signal transduction pathways such as increase of cyclic AMP (cAMP) and of free calcium (Ca++). The dose-dependence, including inverse effects, of several cell functions taken into consideration by our studies are reported in table 2.

We recently investigated the *in vitro* effects of a homeopathic drug derived from extract of *Podophyllum peltatum* (6). Human neutrophils, pre-treated with low potencies (D4) of this drug (final concentration of active ingredient of 0.025 μg/ml), exhibited an enhanced oxidative response to a subsequent challenge with bacterial formyl-peptides. This priming effect was reproduced with purified podophyllotoxin at doses of 0.1-10 μg/ml. On the other hand, doses of pure podophyllotoxin higher than 100 μg/ml inhibited the response, so that the dose-effect curve of the pure toxin showed a typical reverse-U shape: the same toxin causes enhancement of oxidadve metabolism at low doses and inhibition at high doses. It is noteworthy that homeopathic dilutions of *Podophyllum* exhibited only the priming effect on the oxidative metabolism, typical of low doses of pure toxin.

The phenomena of priming, desensitization and inverse effects have been described also in many other circumstances that occur in various cell types, tissues and whole organisms. Example of a tissue priming is the enhanced bronchial reactivity in asthmatics, of organ priming is the hypertrophied heart after repeated exercise, of system priming is the nervous and immune hypersensitivity after challenge with sensory stimuli and antigens respectively. As we will discuss later, this phenomenon is deeply related to homeopathic issues. We got new insights on the general validity of the similia principle when we observed these phenomena in human neutrophils. Our studies 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 well, we were prompted to think to the general meaning of these phenomena in biological systems.

Non-linear dose-response curves are widespread in biology and pathology and especially in immunology and neurobiology. Researchers who are interested in homeopathy are now deserving more attention to these complex phenomena, that are often reported in conventional literature.

Recently we started a new line of research on human platelets and we got preliminary evidence of inverse effects that can be obtained also in this type of cells. The prostaglandin PGE1 inhibits the adhesion of thrombin-treated platelets. However, the same compound is able of stimulating the adhesion of resting (not otherwise stimulated) cells. The possible mechanisms of this phenomenon are under investigation.

The studies of our group are in agreement with a large series of evidence emerging from the literature regarding the regulation of leukocyte functions by cytokines and other compounds. There are many compounds which when administered to macrophages, sti-

mulate them, increasing their functional capacity. Well, many of these compounds (not all) when are administered to macrophages that have been already activate, cause suppression of cellular functions. Therefore, we can see also in this case an example of varying effects according to the cell state of responsiveness.

In our experience, opposite effects of the same agent can be observed in several models (see tables 1 and 2), but the experimental conditions (doses, type of stimulant, cell treatment, cell function) must be carefully set in order to regulate the complex balance of receptors and transduction mechanisms. Therefore, these phenomena at the cellular level should be regarded not as an "universal law" but as an expression of a possible behavior of the living system when it is exposed to suitable conditions.

GATING THEORY

How is it possible that a well known stimulant of adhesion (the bacterial peptide fMLP) becomes an inhibitor of adhesion of LPS-treated cells? Here we propose a model, a theory, that we have called *"Gating theory"*. The concept of gating means that in the sequence of signal transmission inside the cell, some signal have a controlling function – gating – that may enhance or block other signals. Of course, it is worth note once again that this is not the explanation of homeopathy, but the demonstration of how the homeopathic concept of similia principle can be explained on a cellular scale in a precise experimental model. Every model has a value which necessarily is limited to the phenomena that it tries to explain.

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

In figure 2 the same system is shown in the presence of LPS. LPS treatment alone (without fMLP) triggers the adhesion of a substantial number of cells (figure 2A). In these conditions of increased adhesion, fMLP (low doses) works as an inhibitory signal, as a "brake" that inhibits and reverses the adhesion (2B). On the other hand, in the presence of high fMLP doses (2C), the inhibition is by-passed through different, cAMP-insensitive pathways and the adhesion is activated. This may be the mechanism of bi-phasic, non linear

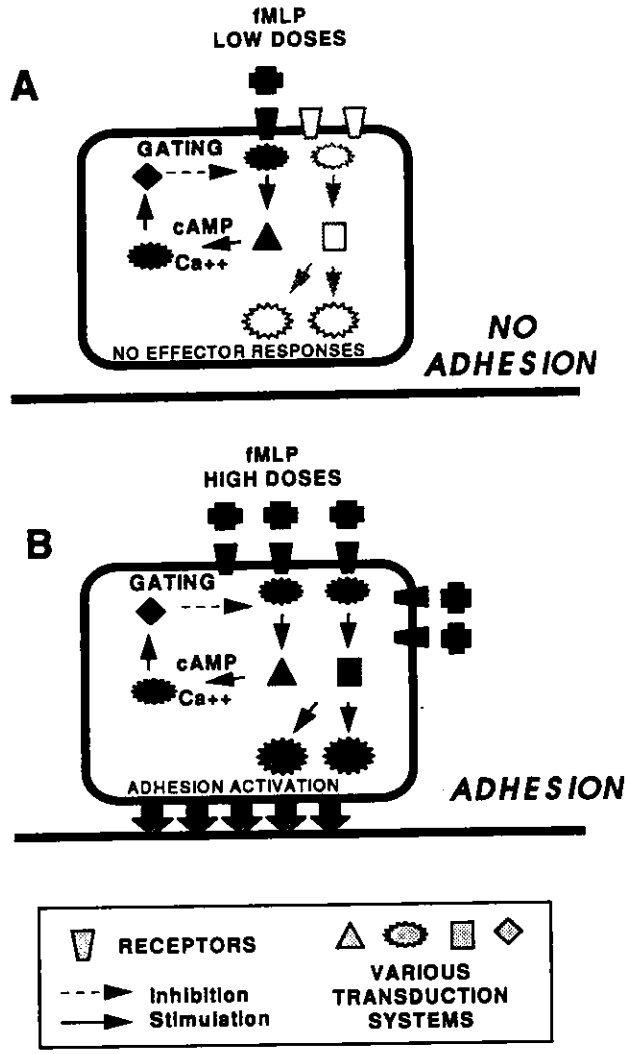

Fig. 1. Schematic representation of the main modifications of a neutrophil treated with low (A) and high (B) doses of fMLP.

dose-dependence of adhesion with respect to fMLP doses that the experiments have pointed out.

Let's draw an analogy with homeopathic 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 (figure 1) and therapeutical effects (inhibition of adhesion) when tested in a sick (LPS-treated) system (figure 2).

This model, involving cyclic AMP as a gating mechanism allows a prediction. If this model is true, by increasing cellular cyclic AMP we should inhibit the adhesion of LPS, even in the absence of fMLP. There are various ways by which cAMP can be increased. We used a system based on the addition of dibutirryl cAMP, that enters into the cell releasing cAMP, plus theophylline, which blocks the enzymes that destroy cyclic AMP. We have therefore done an experiment, whose results are in agreement with the theory: in fact the addition of theophylline plus dibutirryl cAMP inhibited the adhesion (unpublished results). Moreover, we found that low doses of other stimulants, like phorbol esters, which do not cause increase of cAMP, do not inhibit the adhesion but instead stimulate it. There-

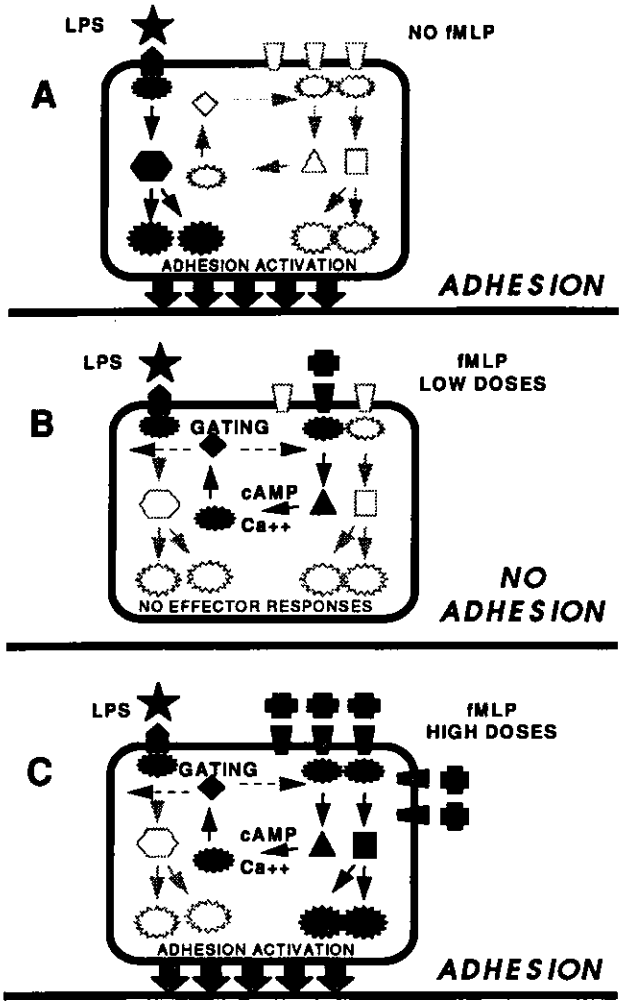

Fig. 2. Model of inverse effects of fMLP on neutrophil adhesion. In the presence of LPS, cells adhere in the absence of fMLP (A). Addition of low doses of fMLP triggers the gating pathway that inhibits adhesion (B). High doses of fMLP trigger both the gating pathway and other transduction pathways, different from those of low doses, that by-pass the gating mechanism and induce adhesion (C). Other explanations are in the text.

fore, it is highly conceivable that the phenomenon of inversion of effect, that is the inhibition of adhesion, is due to the increase of cAMP caused by low doses of fMLP, even if we can't exclude that other mechanisms are involved. In other words, cAMP is a negative signal responsible for inhibition of adhesion.

As we have already said, the gating theory is not the only model that can explain the occurrence of inverse effects at a cell level. Other authors, and in particular the groups of Van Wijk at Utrecht (7) and of Oberbaum at Tel Aviv (8) have put forward different theories, based on heat-shock proteins and on hormesis models. These theories are not in contrast each other, but regard different levels of cell organization. While the model based on gating by cAMP helps 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, the heat-shock protein model helps to understand the experiments where the investigators have used homeopathic doses of toxic compounds like arsenic, cadmium, mercury to protect the cells (renal cells, lymphocytes) from intoxication.

REGULATION OF STRESSED HOMEOSTATIC NETWORKS

Here we report a general model of the similia principle, essentially as described in our recent book (1), with some updating. The model is called *"Regulation of stressed homeostatic networks"* because it is based on the consideration of how the homeostatic networks react to stress and on the possible role of the homeopathic regulation of self-recovery.

Homeostasis

The concept of homeostasis, introduced by the physiologist W.B. Cannon in 1929, refers to all those activities which tend to keep the variables of a vital system constant, or, to be more precise, within acceptable limits. However, also Hahnemann must be mentioned in this respect, because he founded its medical system on the principle of action/reaction: in paragraph 63 of Organon, he outlined this fundamental principle: "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 endeavours to oppose its own energy. This resistant action is a property, is indeed an automatic action of our life-preserving power, which goes by the name of secondary action or counteraction".

It may be useful here to take a look at the homeostatic concept in greater detail, using a schematic model of the type illustrated in Figure 3A. A homeostatic system, in its essential make-up, consists in a *set of anatomical, biochemical, and functional elements designed to maintain a physiological variable within minimum and maximum oscillation limits*. Let us consider a *variable A-A'*, which is in a state of dysequilibrium and in conditions of reversibility due to the action of two *operator or effector mechanisms*, which may bring *A* to the level or condition *A'* and vice versa. The system, however, cannot function properly without some form of control, which is provided by a *regulation center(s)* which receive(s) information from *A'* in the form of a *signal a'* associated with its condition (for example, an enzyme reaction product proportional to how much of *A'* is present or to how much of *A'* is functioning). In addition to receiving *a'* signals (for which it has specific receptors), the control system somehow compares these signals with a *memory* in which the optimal value of *a'* is established. When this value is exceeded, the regulation system is activated and produces the *signal r*, which then inhibits the A→*A'* mechanism and/or activates the *A'*→A mechanism. Usually, these effector mechanisms (enzymes, membrane pumps and channels, but also antibodies or cells of various types according to the systems considered) are endowed with incorporated receptor sites for regulatory signals. The homeostatic system thus consists in a negative feedback loop, in which the information on the result of a transformation or an activity oscillation is fed back in revised and corrected form to the entry point of the cycle.

The model in Figure 3A also considers the fact that the various elements of the system relate to other systems: the signals *a'* and *r* may have effects on other control systems and on other effector mechanisms,

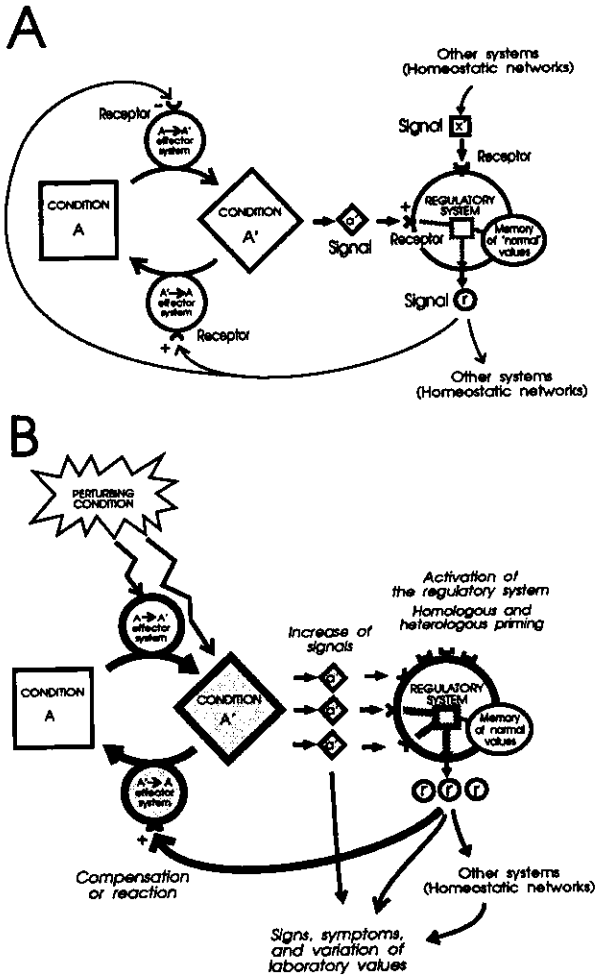

Fig. 3. Schematic representation of a typical homeostatic system (A) and of its modifications under the stress (B). The perturbing condition is posited as being that which acts upon the effector system $A \rightarrow A'$ or directly upon A', leading to an excessive increase in that parameter. With an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

whereas the regulatory system may have receptors for other signals and thus be influenced by these. Therefore, as a general rule, all the homeostatic systems are arranged in the form of *networks* of many elements.

The essential constituents of homeostatic biological systems are therefore the following:

a) *Anatomical or biochemical structures* with adjustable and reversible effector functions. To mention only a few examples, these structures are represented at cell level by enzymes, membranes, contractile proteins, and at body level by the endocrine glands, vessel walls, the cell mass of a certain tissue, etc.

b) *Signal molecules* which enable nearby and remote structures to communicate, such as neurotransmitters, hormones, local chemical mediators, cytokines, physiological inhibitors, and antagonists. A particular complexity feature of the signal molecules is that their message is never wholly specific: the same molecules can be used to communicate between different systems. The same molecules can be produced by many different types of cells. The same molecules can bind to different receptors present on cells in different tissues and organs. There is thus a substantial degree of *redundancy* of biological information, which enables the system to enjoy a considerable measure of flexibility and plasticity, but at the same time makes it difficult to achieve any kind of rigid schematization of the events following the production of a certain mediator in given pathophysiological conditions.

c) *Receptors* for signal molecules or for other types of messengers, endowed with specific affinity and capable of transmitting the signal to other elements of the regulation system. There are membrane receptors, intracellular receptors, and even intranuclear receptors. It should be noted that the receptors are highly *plastic*: the cells are capable of increasing (hypersensitivity, priming) or decreasing (desensitization, tolerance, adaptation, down-regulation) the number of receptors according to their needs, as well as of regulating their activity by modifying the affinity for the signal molecule. On occasion, the cells present more than one receptor for the same molecule, but with different affinities and different intracellular effects.

d) *Transduction systems* that allow coupling of receptor activation with production of signals or with activation of effector mechanisms; this is accomplished by variations of intracellular *second messengers*, covalent and noncovalent modifications of membrane lipids and proteins, and the opening of ion channels. The multiform characteristics of the transduction systems are too vast a topic to be dealt with here. What is beyond doubt, however, is that the level of responsiveness of a certain (control or effector) system is also controlled by such systems in the cell, that they are also modified in the course of disease, and that they are susceptible to pharmacological modulation.

e) *Elements responsible for storage of information* for a given time period: when a system undergoes a change, this may be rapidly and wholly reversible (e.g. the contraction of a muscle), but it may also be a phenomenon which leaves a more or less permanent trace. Usually, though not always, the longer-lasting changes are those which in some way involve the genetic code of the cells.

All the above described elements are interconnected in a complex way, so that a dynamical dysequilibrium is established between them, made of continuous oscillations of the controlled variable values and of mutual regulations. The integrations are of the *horizontal* type, as between cells or between organs, or of the *vertical* type, as between molecular and cell systems, between cell systems and organs, or between organs and the body as a whole.

Stressful stimuli

Let's now consider (Figure 3B) how this model system is modified when a perturbation of a pathological type comes into play which shifts the equilibrium of a given variable A/A' excessively towards A'. The variable A may thus be regarded as the normal condition and A' as the pathological condition, in the sense of an excessive oscillation of the parameter considered. Another possibility is that A' is a pathological event in the sense of the presence of biochemical alterations coming from the outside, i.e. A' is of exogenous origin, such as a foreign antigen or a toxic molecule: the subsequent chain of events does not change. At this point A' produces an enhanced signal a' which then brings about very marked activation of the regulatory system. In analogy with the concept of *priming* introduced

above we postulate that, following an increase in the signal a', the specific receptor system is *primed*, i.e., to simplify things, it exposes a greater number of receptors for a' (see the homologous priming phenomenon mentioned above).

The primed regulatory system increases its activity by producing more of the signal r, which, in turn, will force the effector mechanisms ($A' \rightarrow A$) towards the normal condition A. In this initial phase of the disease, the body reacts logically and efficiently in the direction of equilibrium and healing. For instance, if a' is a molecule "judged" to be abnormal in terms of quality or quantity by the "immune" regulatory system, the system will produce more receptors for a' (in this example, antibodies and T lymphocyte receptors) and more r signals (interleukins, cytokines, interferons) which in turn prompt the effector system (phagocytes or complement) to restore normal homeostasis by eliminating the excess of A' and re-establishing the condition A (healing).

In this initial stage of the perturbation, which might be regarded as perfectly "physiological", other phenomena worthy of note occur: the first of these is the onset of symptoms. *Symptoms are usually linked to the activation of endogenous systems, more than to the direct effect of the etiological agent.* The symptoms thus stem from "side" effects produced by a' activating the specific homeostatic systems. In the diagram presented in Figure 3B, not only do symptoms appear caused by a', but also symptoms caused by other signals (r), produced by the regulatory system. Referring once again to the previous example, an increase in a' and r may cause symptoms stemming from activation of the immune system, linked to the "side" effects of antibodies, complement, or cytokines (fever, leukocytosis, fatigue, sleep, and other manifestations).

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

A second event worthy of note, contemplated in Figure 3B, is the onset of a new sensitivity related to exposure of new receptors by the regulatory system for substances other than a'. This event, too, belongs to the category of "priming" events (heterologous priming) and, in general, to all those modifications of receptor sensitivity and homeostatic system compensatory activity, related to pathological conditions and dealt with in some detail above. The homeostatic systems involved in reactive regulation are thus altered not only specifically by the etiological agent, but also according to a broader spectrum of specificity. This, too, has been clearly demonstrated in many conditions: the interferons produced as a result of a viral or bacterial infection induce a greater resistance to other viruses, other bacteria and even tumor cells; a treatment with barbiturates induces an increase in the activity of microsomal systems in the liver which may serve to offset the effects of other drugs and toxic substances with greater efficacy; when leukocytes come into contact with endotoxins they are also sensitized for other bacterial products; when the main hepatic detoxification system (cytochrome P450) is activated by the chronic intake of toxic substances its ability to metabolize other substances is enhanced. There is thus

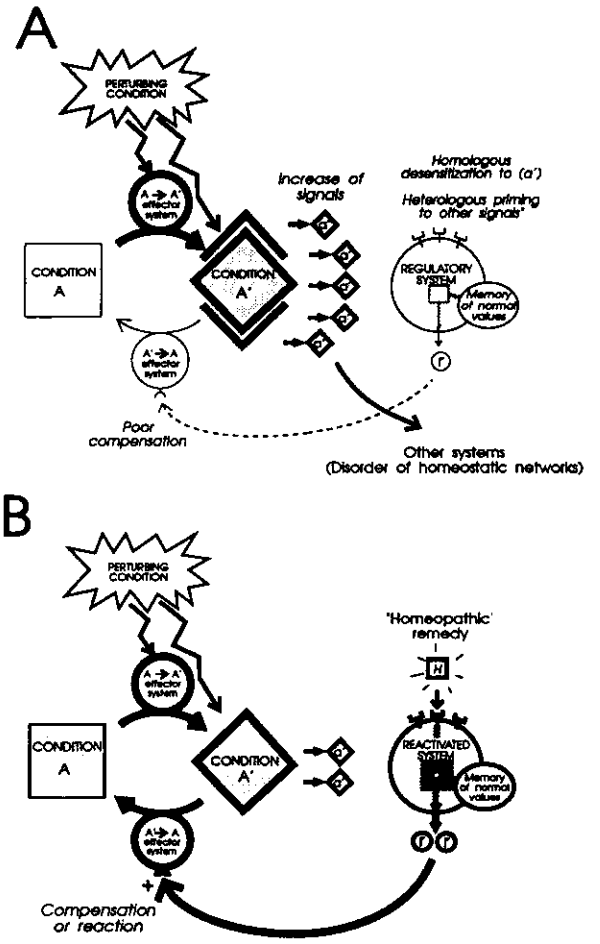

Fig. 4. A: Disorder in a homeostatic system due to persistence of the perturbation. B: Schematic and highly simplified representation of the possible way by which a drug with a "homeopathic" mode of action (*H =) may reactivate the regulatory system and the homeostasis.*

a certain degree of broadening of the spectrum of specific sensitivities in a regulatory system activated during a disease.

Suboptimal recovery and chronicization

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

Therefore, the second phase of the homeostatic reaction to a stressful stimulus is represented, in schematic terms, by homologous desensitization, by the decrease of responses to a stimulus after repeated stimulation. 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. This phase can be considered as the biological representative of the phenomenon of chronicization: the homeostatic unbalance (the true disease) is now self-maintained due to the suboptimal response by one or more homeostatic systems.

The important thing to note is that self-maintainment of the disorder can continue even if the starting agent is no more 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 "attractors", or attractor basins. The system can be set in an attractor, can "learn" and consolidate this "pathological behavior" and thus be unable to find the "right way" to change towards the healthy, primary, behavior.

With reference to figures 3B and 4A, one can see that the regulatory systems that have been "recruited" by the increased signals, i.e. the regulatory systems that are involved in the disease, exhibit new and marked sensitivity to other signals. In the following section we will show how these new sensitivities, triggered by the disease process, may serve to detect the modalities by which the disease is expressed (i.e. the significant signs and symptoms). According to the homeopathic procedure, this is very important because through the application of the similia principle, also the right remedies should be detected.

Homeopathic regulation

After having reviewed the major dynamical events occurring in a model of a typical disease, the question arises of *how to stimulate the recovery of the homeostatic communication* that has been blocked or deviated. According to our model, the regulatory system should be stimulated through primed sensitivities, not through the receptors for "*a*" signal. So we should bypass homologous desensitization and utilize other sensitivities of the same system to push the homeostatic balance in the right direction. This is not a possibility for homeopathy only, but a rational approach that is followed also by scientific, "mainstream", modern medicine.

Modern pharmacology has discovered a wide series of molecules acting on homeostatic systems. We can have these molecules in vials and we can deliver them to the patients in the attempt to induce the recovery from the disease. Modern therapies that are founded on this principle, using low doses of biological compounds to stimulate the recovery of the homeostatic system are the cytokine therapy in the immunocompromised host, the use of endotoxins as immunostimulants, the treatment of immune disorders with immunoglobulins, the use of nitric oxide in respiratory diseases, the administration of oral myelin in multiple sclerosis or of oral collagen in rheumatoid arthritis, the use of bacterial extracts in recurrent bronchitis and of oral allergens in allergic diseases, the therapeutic vaccination to cure cancer. Moreover, we can refer also to the use of soluble receptors and in general to the new branch of pharmacology called peptidomimetics.

There is also a number of animal models based on this principle. One of them was developed by dr. Anita Conforti in Verona in collaboration with us (7), showing that injection of low doses of immune adjuvant (based on killed *Mycobacterium butyricum*) in peritoneum to rats is able of preventing and cure the arthritis induced by the injecting of high doses of the same Adjuvant into the paw.

It is important to stress that most of these therapies are still at the experimental stage and that while the general principle on which these therapies are founded is known, that is the stimulation of endogenous healing mechanisms, the physiological and biochemical details by which these therapies act are far from to be clarified In many instances one can read in reports that the therapies work but that nobody knows how they do work.

The main problem, however, is the following: do we always know the primed receptors and their specific signal molecules in each individual case of disease?

As a matter of facts, 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 proper specific molecules to be supplied. If we deal with blood glucose concentration, we need only a couple of 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 out the right stimulant or the right inhibitor for the involved systems (assuming that these latter are known).

Modern medicine has accumulated a lot of knowledge about the molecular bases of diseases, but often it is not able to understand exactly what is happening in the dynamic of complex homeostatic systems of the affected subjects. In a few words: the doctor often doesn't know what to give to the patient in order to get the most suitable regulatory effect, he or she doesn't know which type of regulatory molecules and which doses of them could be useful to his or her particular patient in that particular moment of the evolution of disease. This is particularly true when dealing with personality profiles and subtle functional disorders, but we know that these have a great impact on the health of the individuals. How can we correct them? We suggest that in these cases the application of the similia principle may be appropriate for the following reasons.

By reference to our basic model, which by the very nature of things is necessarily highly simplified, we are in a position to postulate the mode of action of the homeopathic remedy (Figure 4B). It *activates the regulatory system via receptors other than those for* a', *but which produce the same effect, namely that of restoring production of the signal r and thus of bringing about activation of the compensatory mechanism* $A' \rightarrow A$. The homeopathic drug is therefore thought to act in lieu of *a'* to which the system is no longer sensitive as a result of adaptation.

In this model, therefore, the homeopathic drug is postulated to interact with the regulatory system(s) concerned in the pathological perturbation of the homeostasis, because it has been identified precisely on the basis of its *ability to cause symptoms similar to*

the disease, i.e. symptoms similar to those caused by the mediator a' via activation of the regulatory system. It is clear that, since most of the symptoms in a pathological condition are due to activation of homeostatic reaction systems, it should be possible somehow to "reproduce" the activation of these same homeostatic systems by administering a compound which "reproduces" the symptoms of the disease in a healthy and sensitive subject. Theoretically, in the healthy, nonperturbed system, *symptoms similar to those of the disease* may be produced by the administration of *a'* and *r*, or of a substance which activates the regulatory system via receptors other than those for *a'*.

In the diseased system, *a'* is already present in large amounts, but, if the mechanism of receptor adaptation comes into play, we may find ourselves in a situation whereby the regulatory systems become "paralyzed," prove inefficient, and are themselves unbalanced. Since, however, the regulatory system conserves other sensitivities in the disease state, and indeed probably *accentuates them* (see the priming phenomenon), if other sensitivities are brought into play through other signals, the system can be reactivated. *By subjecting the regulatory system to a signal "similar" to a' (in the sense that it causes similar symptoms), the response r is elicited and thus a return to normal homeostasis.* The *similarity* is therefore between the symptoms caused by the activation of reactive mechanisms by the disease process in the patient and the symptoms caused by activation of the same reactive mechanisms in a healthy subject by a biologically significant external agent (in this case, the homeopathic drug).

After having tried on healthy systems several drugs and after having identified a specific drug that causes that typical pattern of symptoms (*"provings"*), we can assume by hypothesis that in a person affected by a natural disease (lack of homeostatic communications) that specific drug will help the homeostatic systems to recover the homeostasis by introducing the correct information. The remedy will slightly stimulate the regulatory systems using receptor sensitivities different from those that are blocked by the disease and this is exactly what the whole system needs to recover from the disease. If the starting stressing factor is no more present, the network will eventually find the way to reenter in the previous attractor and thus to become finally ad definitely healthy.

CONCLUSIONS

In synthesis, the hypothesis put forward here is based essentially on the following points:

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

b) As long as the disease process does not lead to excessively profound and irreversible impairment of the regulation systems, *this blockade can be by-passed using different receptor sensitivities* (for exogenous or endogenous substances) which the perturbed systems themselves conserve or even accentuate.

c) The identification of suitable substances for reactivating the homeostatic systems *specifically* blocked in a given disease process is hard to achieve *with precision* in any single patient by using the conventional scientific approach, on account of the complexity, variety and multiplicity of the systems involved and because of the dynamic and changeable nature of diseases.

d) The homeopathic approach, particularly through the use of analogy (law of similars) *makes it possible to get nearer to identifying substances capable of interacting specifically with the homeostatic systems involved* in the disease process in each individual case.

This is the "genius" of classical Hahnemann's homeopathy, but it shouldn't be seen in contrast with modern, scientifically-oriented molecular medicine. The two approaches are not in contrast: mainstream pharmacology uses a *structural* analogue, identified as the right molecule for the right receptor or for the right target system (if they are known). Classical homeopathy uses a *functional* analogue. We call it functional because it is identified by the function that it exerts on the target system, its function is to cause the appearance of symptoms in healthy subjects and the reinduction of homeostasis in sick subjects.

Mainstream pharmacology may be more precise when the exact mechanism of the disease is known and specific remedies can be administered. Homeopathy may more effective when the complex, subtle and individual dynamics of the disease are considered. In fact, the careful analysis of symptoms and the application of the similia principle may by-pass our ignorance of the molecular details of the regulatory homeostatic networks. Functional analogy can be used also if we don't know exactly the receptors and the target system into the complex network of homeostatic systems.The classical homeopathic approach, based on the symptom analysis, may have a number of advantages: *a*) symptoms are the expression of the typical reaction of individual homeostatic systems; *b*) symptoms appearance is very sensitive and is often the earliest manifestation of a homeostatic disorder, *c*) symptoms language is psycho-somatic and complex by its nature, it can be used also as a symbolic language of the body; *d*) symptoms analysis is very cheap.

Taken together, these considerations lead to the suggestion that homeopathy is a rational exploitation of homeostasis rules in complex systems. Of course, the clinical applications of similia principle may also present potential risks that have to be taken into account, the main of which could be to leave undiagnosed and untreated severe diseases that do not present specific symptoms. Since we are dealing with the complexity of the human being, it is very important to consider this method as an experimental and hypothetical approach, not as a result of dogmatic rules. If this *caveat* is taken into consideration, homeopathy could probably represent for the modern physician a possible option and a guide in ultra-complex level, dealing with the intimate nature (the *"internal essential nature"*, as called by Hahnemann) of diseases. Only well conducted clinical studies can confirm this hypothesis.

In this work, we have not dealt with the problem of dilution/dynamization and other highly controversial questions raised by homeopathy, but we have focused our attention on the possible biological basis of the principle of similarity, which is being increasingly utilized also in modern mainstream medicine. Histori-

cally, the principle of similarity is the first "law" and the basis of the homeopathic method. We and others (8-10) have shown that from a scientific standpoint, the pnnciple of similarity can be investigated and understood independently of the so-called "high dilution" or "high potency" effects. In cellular models and in animals, the principle of similarity can be found to be consistently and reproducibly operative when using low-medium doses of biological compounds, even if we should remember that several laboratories have also described biological effects of highly diluted/succussed homeopathic solutions (for a recent review, see ref. 11).

Moreover, it should be pointed out that many homeopathic drugs that are marketed contain significant amounts of active compounds: at least for these formulations, the "conventional" molecular paradigm can be utilized. In any case, we suggest that the substantial meaning of the principle of similarity as it is proposed here does not change if the information transfer between the "drug" and the body occurs either through strict molecular interactions or through molecular interactions based on the postulated permanence of physical structures or frequencies capable of carrying and transmitting information in highly diluted/succussed solutions. We have extensively discussed elsewhere (1) the accumulating evidence that the transfer of biological information, including receptor and enzyme regulation, may have both a chemical and a physical nature (even if the latter is admittedly much less known).

The scientific and rational understanding of the principle of similarity, which is undoubtedly one of the most interesting lines of thought in the history of medicine, represents the basis for new experimental projects aimed to clarify apparently paradoxical findings and for establishing a more fruitful dialogue between different medical approaches inside the only one medicine.

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THE UNIVERSAL LANGUAGE OF SYMBOLS IN THE PATHOGENESIS OF HOMEOPATHIC REMEDIES

KEY WORDS: Symbol - Archetype.

The Turin School of Hahnemannian Homeopathy seeks to integrate the classic Hahnemannian teaching with holistic trends of thought which tackle the mind – body question. We consider that to address this theme it is fundamental to use symbols.

Symbolic thought as an intermediary between finite processes and in-finite processes, between body and mind, between matter and spirit is also in fact the constituent,structural basis of traditional Chinese acupuncture of a Taoistic philosophical derivation.