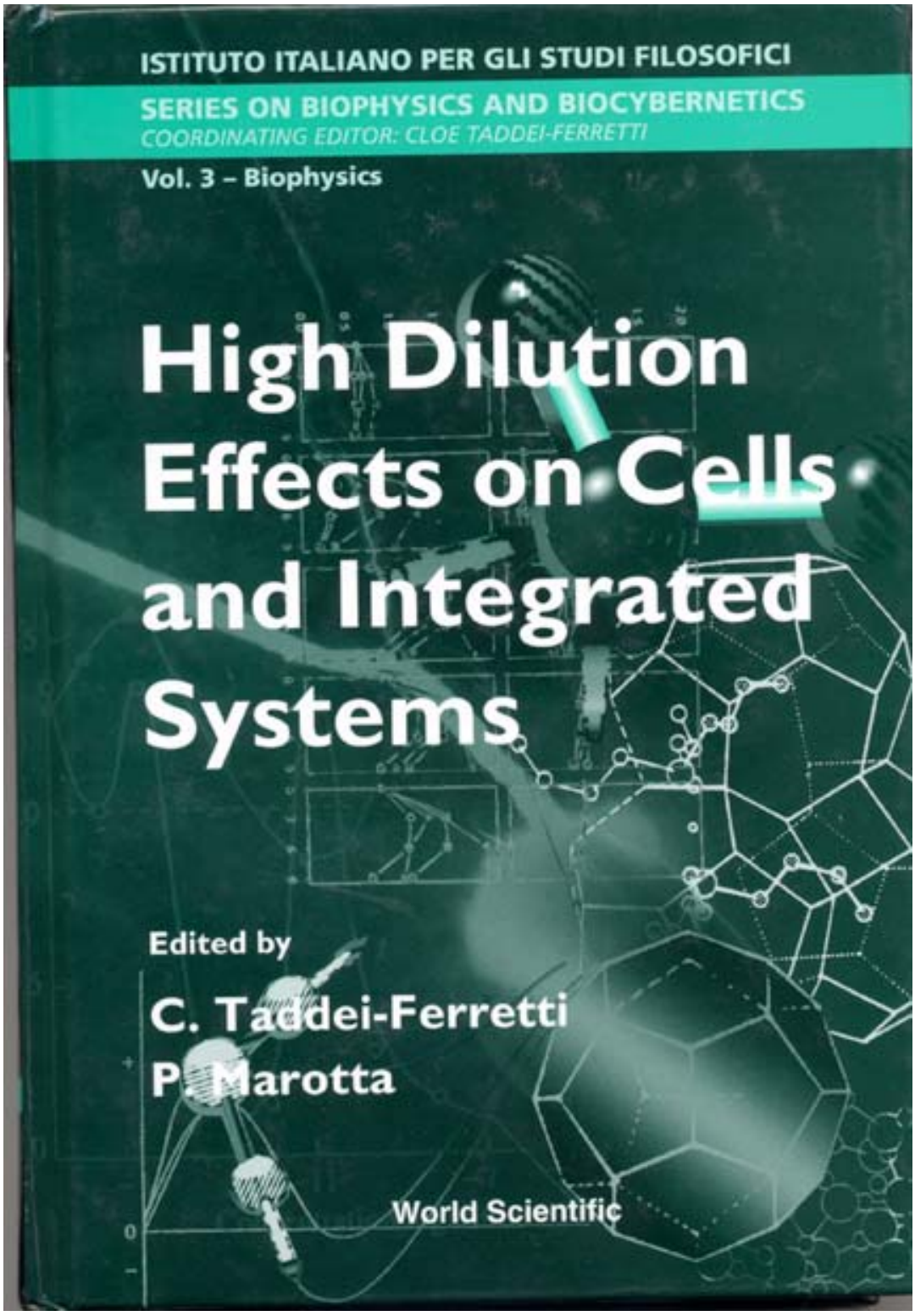
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BASIC RESEARCH ON HIGH DILUTION EFFECTS

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ABSTRACT

Basic research on high dilution effects started with homeopathic therapy. So many models have been tested that we have tried to classify them according to the general concept of regulation. Firstly, succussed dilutions must be separated from unsuccussed very low doses from a physical point of view. This leads us to discuss the validity of the controls in high dilution research. Then, following a classification according to regulating effects, one can consider that some research in the field of "homeopathic research" can be relevant to cybernetic regulation and, in some cases, very low dose effects can be described as cybernetic regulatory signals. Hormetic models and application of the Arndt-Schultz law are based on the identity principle and are related to variations of concentration. They are presented and differentiated from the self recovery process which exists as a function of time. By using unsuccussed molecular and succussed non-molecular dilutions, the hormetic model supports a learning process which must be related to informative concepts. Starting from this primary level of informative process and by comparison with the phylogenic evolution of the immune system as an informative system, we can elaborate a progressive information organisation of the high dilution effects. Endogenous molecules have a specific regulatory function while highly diluted exogenous molecules will only be informative in the framework of the similia principle.

1. Introduction

Studies on the effects of high dilutions started with homeopathic therapy. Without such an example, no scientist could imagine to test such diluted substances that theoretically contain no molecules. It has been proved by therapeutical use that extremely diluted solutions even beyond Avogadro number could have biological effects. This is a very controversial affirmation which has been considered by the scientific community as a scientific error. It looks like an error because nobody is able to explain why and how these high dilutions can work. However, experiments investigating this phenomenon have been performed by various scientists, most of them attempting to prove the effects of homeopathy.

Since many papers have been published, this work does not claim to list exhaustively all published research. The proposed models are so different and the results so various that it is necessary to clarify the subject. Many classifications can be proposed: we prefer trying to classify them without any chronological approach but by ordering them according to their relationship with the general concept of regulation. After describing rapidly the physical properties of such high dilutions, we propose a classification according to cybernetic regulation, hormesis, the Arndt-Schultz law and a new paradigme which implies the communication between living bodies by receiving signifying information.

2. Physical studies of high dilutions

The physical properties of high dilutions have been studied. A high dilution is a solution of a material (pure chemical or biological substance, vegetal or biological extract etc...) serially diluted with succussion between each dilution in a solvent, classically water or water+alcohol. This is also called potentised dilutions. The physical modifications of the potentised solutions have been tested by NMR by Demangeat *et al* [1, 2]. It seems that the succussed diluted solution presents significant differences compared to the succussed water control allowing the hypothesis of a remaining modification related to the original molecule. Apart from these two works, no scientific repeatable study has really been performed [3]. Two approaches may be proposed: the structuralist one, derived from the mechanistic paradigm, demonstrating a conservative structure of the original molecule printed in the solvent [4, 5, 6]. The second one is based on the diffusion of an informative carrier from the succussed solution. This information has been transferred by Endler *et al* [7] or Van Wijk *et al* [8] either through glass from a sealed phial , or as an electromagnetic signal by mean of an input coil linked to a filter and an amplifier by Endler and Smith [9]. The high dilution signal of histamin transmitted to an isolated guinea-pig heart has been inhibited by a magnetic field [10]. Our personal observations of pharmacological activities of the succussed solvent (compared to the unsuccussed solvent) in some biological models prompt us to think that the succussed solvent is a modified structure avid to trap information from inside or outside the body of the receiver.

We must ask ourselves now whether the true control of a succussed high dilution is the succussed solvent. We will demonstrate in an other chapter [11] that the solvent plus a substance X, once diluted and succussed, becomes a new substance X (the potentized substance X) which is different from succussed solvent + succussed substance. This observation is important considering the controls to be used to test pharmacologically succussed remedies, the true control being the unsuccussed remedy or the unsuccussed solvent.

3. Pharmacological experimentations related to cybernetic regulation.

Firstly, we understand now that the dilution-succussion is a fundamental modality to obtain pharmacologically active high dilutions. We will distinguish this kind of preparation even though they contain still molecules i.e. diluted less than 10C (10^{-20}) from the unsuccussed very low concentrations. We can find in classical research either

very low concentrations of pheromons which act at the level of 10^{-16} M [12], or neuropeptides introduced directly into the brain at 10^{-6} pg[13], or kinds of catalytic effects of metal at picomolar concentrations[14] or immunomediators at 10^{-14} M[15] or neuropeptide activity on lymphocytes [16] as examples. No comparison with the effects of succussed high dilutions is available.

The pharmacological effect may be related to the presence of molecules. Some models published on "very low dose effects" are only related to a cybernetic regulation as a signal function. Two kinds of work presented as "very low dose effect" studies for the demonstration of the activity of low succussed dilutions have been published. Bonavida *et al* [17, 18, 19] demonstrates the synergistic activity of a cytotoxic cytokine, Tumor Necrosis factor α (TNF α), and cytotoxic drugs such as adriamycine or cis-platinum , or microbial toxins. To summarize, they demonstrate the increase of the cytotoxic effects by association of very low doses of TNF α(in a range of 6 to 600 picomols when associated with 0.1 to 10 nM of diphteria toxin). These concentrations are normally inactive. Bellavite *et al* [20, 21] report the reverse effect of a formylpeptide chemotactic substance (fMLP) on various phases of activation of human blood neutrophil granulocytes in vitro. The two concentrations giving opposite effects were 1-5 nM (low) and 100-500 nM (high). These two kinds of research are an excellent example of the confusion between cybernetic regulation as a function of a signal-molecule allowing modifications of the regulation (maybe by enhancing the cAMP formation in the cells by using the toxin in the TNF model). We are strictly in the cybernetic information network with a signal effect. In this case, only low potencies are active. The cybernetic regulation requests signals given at molecular level. Moreover, these are two "in vitro" models and no examples of this kind exist by using pharmacologically "in vivo" such *unsuccussed* low concentrations.

4. The self recovery, or rebound effect.

There exists a phenomenon of inversion of effects as a function of time in the same individual which has received the stressor. We observed that immunosuppressed BALB/c mice by 100mg of cyclophosphamide show a very low lymphoblast transformation test (LTT) induced by mitogenic substances 2 days after the challenge, but an opposite effect is observed 10 days later when the LTT of the treated mice becomes statistically superior to the control mice. Arinaga demonstrates that a single dose of cisplatin in cancer patients stimulates the cytokine production of peripheral blood monocytes [27]. This self-recovery is also called the rebound effect and is the consequence of the immunosuppressive effect. It is a biological phenomenon which exists as *a function of time* after a strong pharmacological or toxic effect as shown in figure 1: the organism presents the opposite manifestations

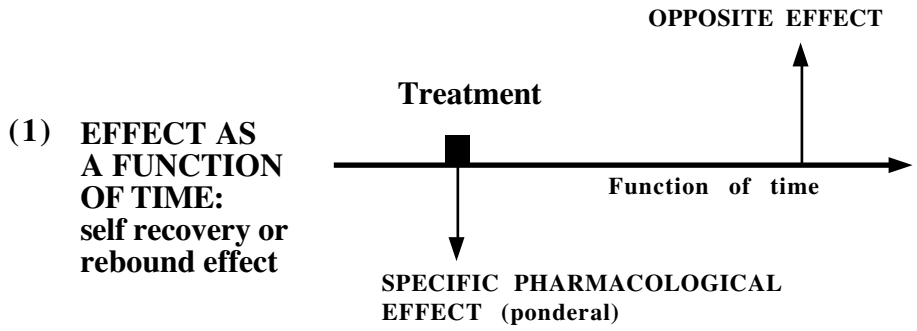


Figure 1 : Self recovery or rebound effect

as a dynamic reaction against poisoning. It is not related to a general immunological mechanism (except in an immunosuppressive effect) and has no relationship with the placebo. This self-recovery is the reaction of the living body to aggression and self-recovery uses the appropriate and specific tools to reach a new equilibrium after the aggression . The forces it uses in order to find a new balance are so strong that they go beyond the final equilibrium.

5. Experimentations in the hormetic model

5.1. General principle of hormesis.

The modern notion of hormesis originated with the observations of Southam and Erlich[22] and was developped by Stebbing [23]. Hormesis has no relationship with the similia law which is one of the characteristics of homeopathy. Hormesis is a very well known phenomenon which demonstrates the reverse toxic action of a substance which becomes a stimulating agent at a lower concentration (figure 2).

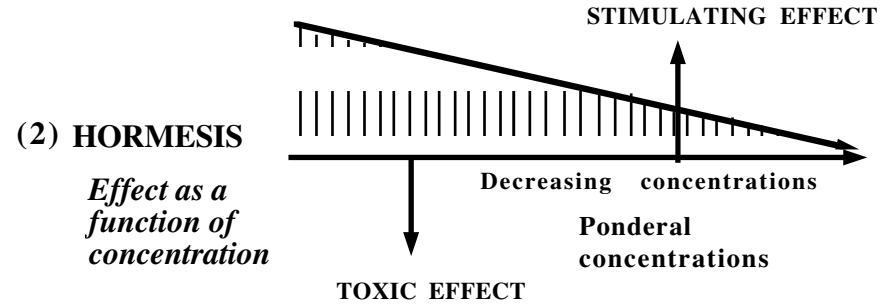


Figure 2 : Hormesis

This was demonstrated with ponderal doses, the reversion of the effect being obtained only by a small decrease of the concentration (10-100 times lower). Models have been created with various poisons and on all possible organisms whatever their level in evolution, from procaryotic cells to plants, from eucaryotic cells to mammals (see the review by Oberbaum *et al*, [24]). This reverse effect was demonstrated even with very low doses by Wagner *et al* [25] who showed that the concentration of 25 μg of vincristine, a cytostatic remedy, inhibited the growth of lymphocytes while 1pg stimulated the cold treated cells.

5-2. The Arndt-Schultz law and the generalisation of hormesis.

The demonstration of the reverse effect as a function of concentration is an ancient notion proposed in 1877 by Schultz [26]. Arndt at about the same time wrote that "weak stimuli slightly accelerate the vital activity, middle strong stimuli raise it and very strong ones halt it "[24].

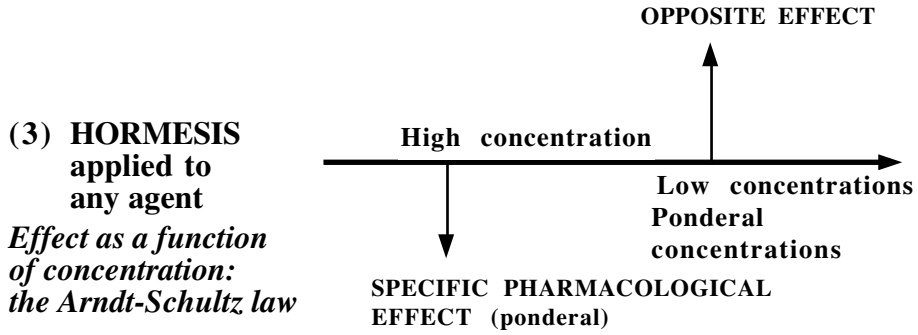


Figure 3 : Arndt-Schultz law

We can propose a kind of generalisation which seems to be a general phenomenon whatever the substances (figure 3). For example, high concentrations of caffeine both stimulates and depresses respiratory centers; chemicals, alcaloids, metals etc.. are listed in manuals of Pharmacology with indications of the opposite effects observed as a function of concentration.

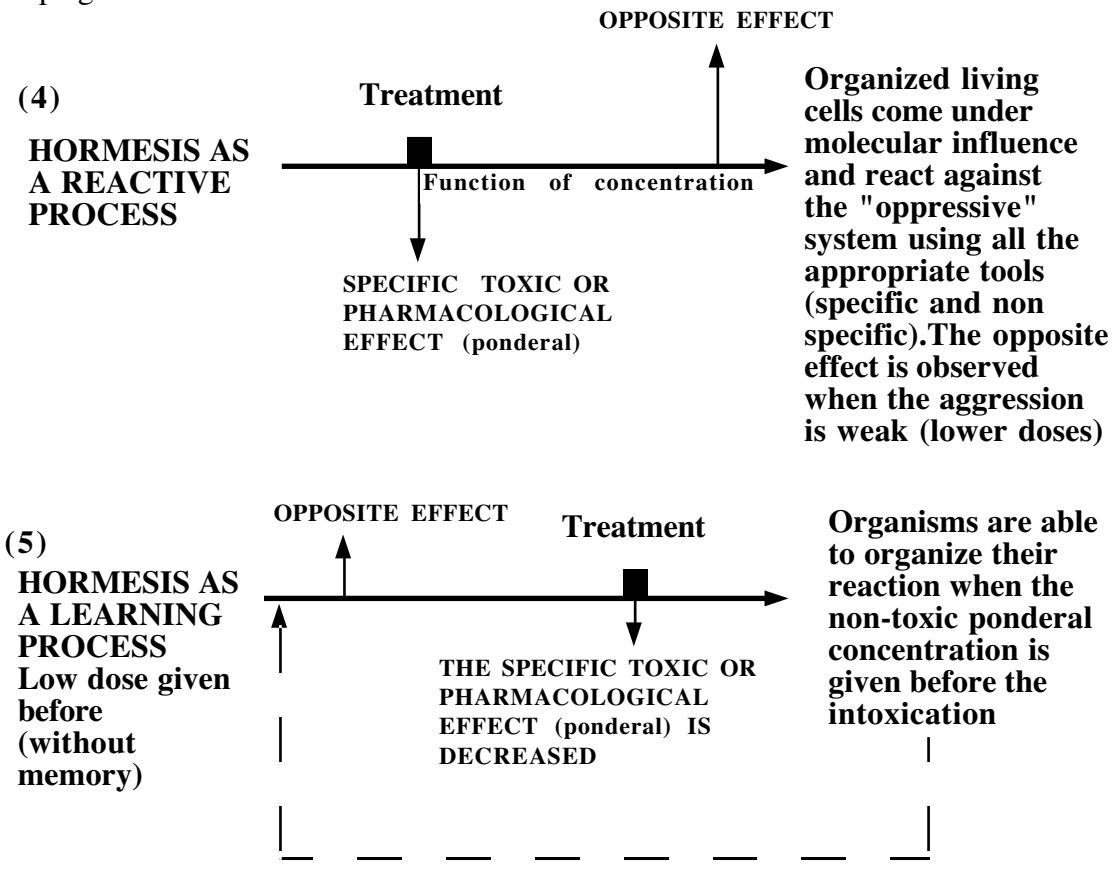
5.3. The application of hormesis: the principle of identity.

The administration of low doses of a poison to an organism teaches it how to fight against the same poison. The famous king Mithridate, using daily small doses of various poisons, could not be poisoned and died by a sword-thrust. The protection is strictly given by identity between the pretreatment and the poison and is strictly specific (figure 4 and 5).

Pretreatment by low concentrations of poison have been used in cell models, in various living organisms. Heavy metals have been used, or arsenite, or many other products. Weis *et al* [28] showed that, after cadmium intoxication of fish, fin regeneration occurred more rapidly if a pretreatment with a lower dose of cadmium had been applied. Van Wijk et al [29, 30, 31] tried to analyze the general cellular adaptation

syndrome by using cellular models. All the events described concern the adaptative process during the cell cycle after toxic (arsenite) treatment related to the action of heat shock proteins. All the mechanisms described are of interest and the action on the cell cycle is very well done. Another recent example is given by Conforti et al [32] in an immunological induction of arthritis in rats by injection of Freund adjuvant (*Mycobacterium butyricum* associated to paraffin oil) into the hind paw. Lower doses (10 to 100 times lower) of adjuvant injected intraperitoneally starting 6 days before the arthritogenic injection or 10 days after significantly decreased the arthritic process. The general observation of a stimulation of life and longevity has been observed after hormetic stimulation by toxic substances[33].

We propose that pretreatment allows a learning process aimed to establish a protection against the "waited danger". Specific appropriate tools are conceived and performed by the living organism in order to fight against the aggression. When the low dose is given after the toxic challenge, it allows an amplification of the organized defence, helping its achievement.



Figures 4 & 5 : Hormesis applied to the principle of identity « mithridatization » using molecular concentrations

5.4. The principle of identity applied to high dilution effects

The same observations have been made by researchers using succussed high dilutions of the poison itself (figure 6). This may be observed either with pretreatment or after poisoning: in the first case, the living organism is, as before, in the situation of a learning process; in the second case, the defence is increased by an addition of information. Succussed high dilutions are supposed to be an informing structure. Examples of protection by succussed high dilutions of heavy metal are given [34, 35] by using 10^{-30} or 10^{-40}M of mercury chloride**.** Taddei *et al* [36] study the effect of high dilutions of different teratogenic substances administered before and after the teratogenic challenge. The results demonstrate the specificity of the principle of identity as the best results preventing caffeine teratogenic effects were obtained with coffea; however the adenine did not protect against the adenine itself.

Doutremepuich *et al* [37, 38] have shown in vivo and in vitro that high dilutions of aspirin had a thrombogenic effect whereas classical ponderal doses have an antithrombogenic effect. The same principle of experimentation is presented by Pongratz on plants [39] by using.silver nitrate to stimulate the growth of wheat.

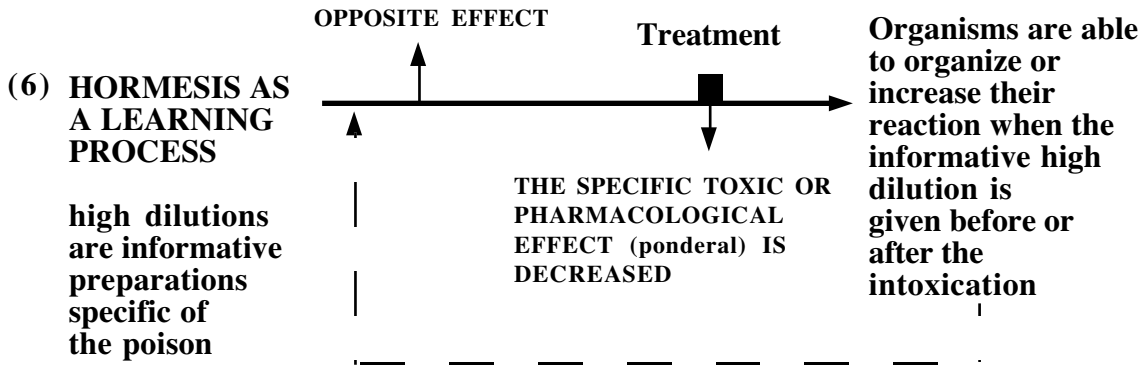
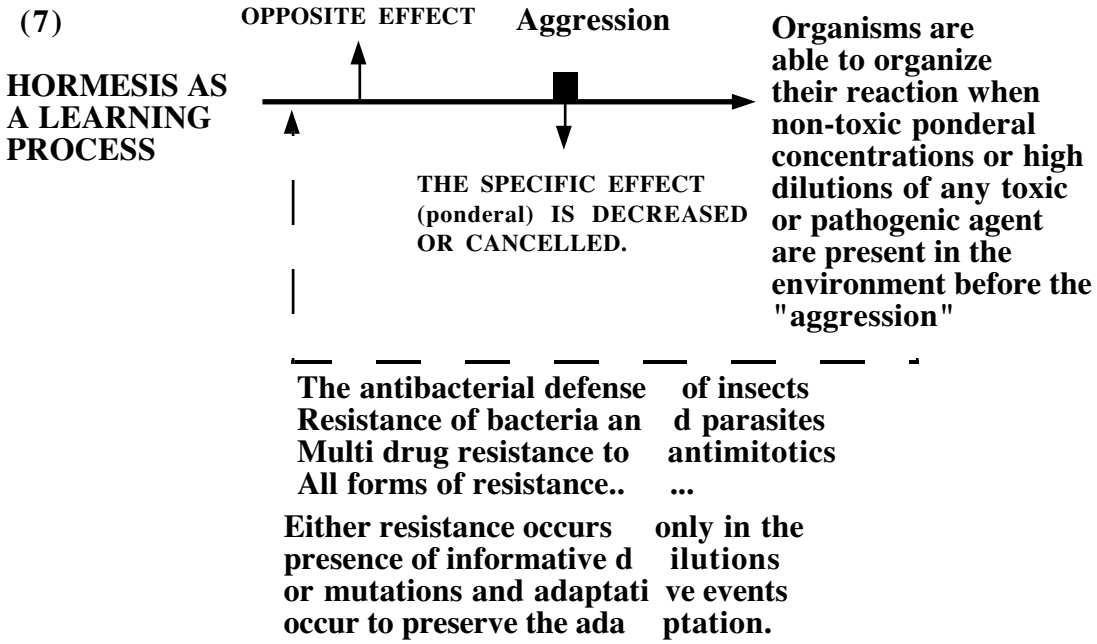


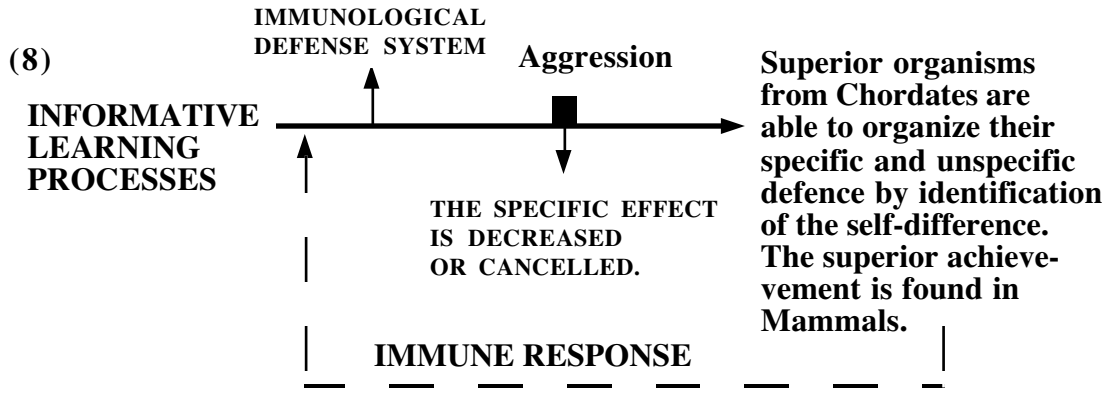
Figure 6 : Principle of identity using high dilution of the poison in a warning process.

6. From the hormetic learning process to high level informative learning processes: model of the immune system phylogenesis.

All forms of resistance seem to start with hormesis, this kind of primitive learning process which functions in all living organisms, from procaryotic cells to the most achieved mammals as Hominidies. We can propose that the resistance of bacteria to antibiotics, the resistance of parasites, the resistance of malignant cells to antimitotic substances (multi drug resistance) could originate in an hormetic model, a real learning process depending on the informative recognition of these poisons. The "memory" could be either a permanent presence of informative structures in water, for instance, and no true memory would exist or an induction of genetic mutations which would preserve the momentaneous adaptation. This kind of evolution does not belong to strict darwinism.

Starting from the hormetic model as a general law of defence of living organisms, it is interesting to analyse the evolution of the immune system which r nd specialized protective organisation of living organisms against pathogenic aggressions. The first organisation which appeared and which is preserved in the most ancient evolutionary branch of arthropods represented by insects belongs to the hormetic model (figure 7) [40]. The first observation of Metalnikoff [41] in 1920 demonstrated that caterpillars infected by bacteria were protected if they had received just before infection a small injection of the same bacteria. No memory was observed. The defense was non-specific. We now know that anti-bacterial peptides are induced by the first contact. No true immunological memory occurs (the true memory-lymphocytes only start with Chordates apparition when true lymphocytes with recognizing molecules appeared).





Figures 7 & 8 : the principle of identity applied to defence systems

It is interesting to compare the immune defence of insects to the immune defence of mammals (figure 8). Mammals possess a recognizing structure allowing identification of the self represented by the Major Histocompatibility Complex (MHC). The receptors of thymic lymphocytes are able to identify the "self difference": this phenomenon describes the fact that as long as T cell receptor is faced with a self structure alone such as MHC associated with a self antigenic peptide, the lymphocyte

remain neutral. The moment it identifies a difference i.e. the presence of an external antigenic peptide different from the self associated to the MHC, the immune system is activated.

If we compare these two extreme systems of defence, the archaïc one as hormesis with a very simple learning process, no memory, and the achieved one, analysing the self, recognizing the "difference", with a strong physical memory, we can identify the evolution of organization structures able to perceive and treat information." According to the Bateson's definition, information is "a difference which makes a difference" [41].

7. Experimental models using high dilutions of endogenous molecules.

Following the model of evolution in the informative sytems allowing the preservation of the species, we can now evoke other informative models using high dilutions belonging either to the self such as endogenous molecules, or not belonging to the self as exogenous molecules. It is easy now to understand that a framework for understanding is necessary in order to observe an "effect" of this information. Many experimental models have been carried out with endogenous molecules, most of them relevant to the immune system. Descriptions of an immunomodulatory activity of succussed dilutions of bursin or thymulin are described in this book [43, 44, 45, 46]; higly diluted histamin even placed in sealed vials or the highly diluted antigen itself was administered in isolated hearts of guinea pigs immunized with ovalbumin induced significant coronary flow variations [47, 48, 49]. Thyroxine was administered in highly diluted succussed solution (10^{-30}) to frogs at the end of the metamorphosis. Significant modifications of the motility were observed by Endler *et al* [40, 51]. In these models, high dilutions bring information of endogenous molecules which are automatically recognized by the living organism (whole body or organ). The effects of this endogenous molecule information belong to various mechanisms according to the nature and the level of information and the state of the receiver. A dilution-dependent effect characterizes a high level of information.

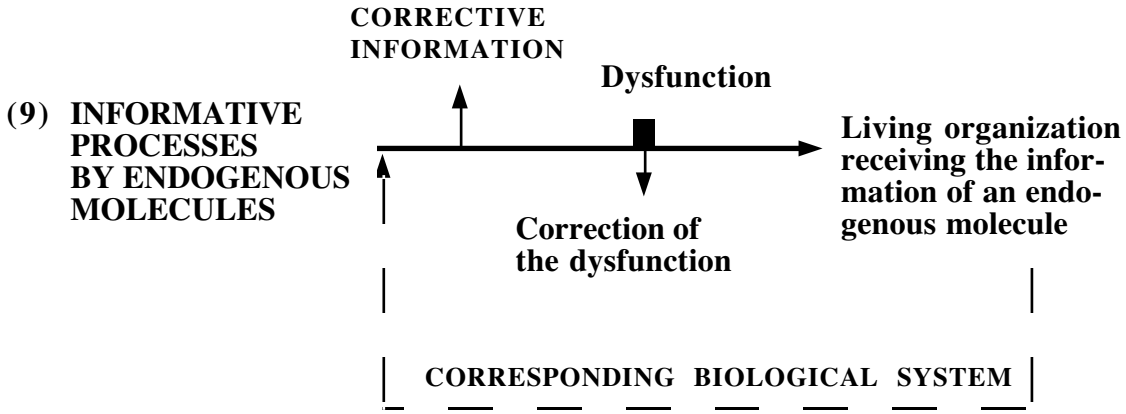


Figure 9 : Effect of high dilutions of endogenous molecules

8. Experimental models using high dilutions of exogenous molecules.

These models are based on the similia principle. Experimental models of this type are rare: they require the similarity between the symptoms of the remedy and the pathology as in the Oberbaum model [52, 53]. Results could be compared to the therapeutic effect in homeopathic therapies. The information of the remedy is able to modify the subject itself by switching to a"new" normal state [11]. In these models, we only use the image of the remedy's symptoms.We need neither identity between poison and high dilution of the same poison nor pretreatment as in hormesis. These models clearly belong to a different approach which relies on signifying communication at the level of the living body [11].This is exactly what we call the homeopathic model.

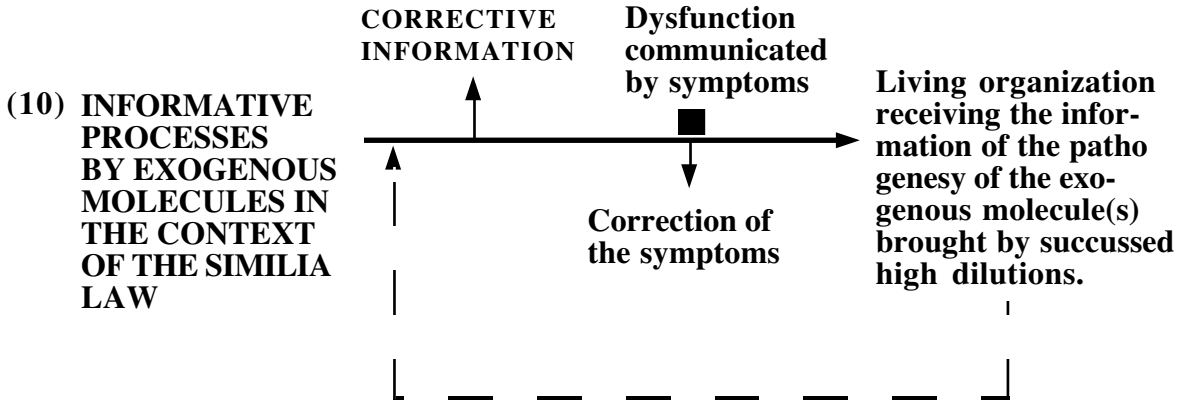


Figure 10 : Informative process in the similia law

9. Conclusion.

Basic research on high dilution effects leads us to consider many possibilities of regulatory mechanisms because a succussed high dilution is the carrier of information corresponding to the original molecule. These regulation modalities are specific to living organisms able to receive and treat information. As we demonstrated in this chapter, the hierarchy of theses processes begins with the mechanistic cybernetic regulation using signal-molecules to reach very sophisticated informative modalities. The particularity of this hierarchy is a non-analytic model, different from the fractal model: we have established an integrative hierarchy in which each level is included in the following superior level. Moreover, this information is more and more significant for the body from the first to the last step, demonstrating that the more complex the biological system , the more specific and more significant is the information. We started from the molecular signal in cybernetics and reached the image in the similia principle.

References

[1] J.L.Demangeat, C.Demangeat, P.Gries, B.Poitevin, A.Constantinesco, "Modifications des remps de relaxation RMN à 4 MHz des protons du solvant dans les très hautes dilutions salines de silice/lactose", *J.Med.Nucl.Biophys,* 16, 2,pp 135-145, 1992.

[2] J.L.Demangeat, P.Gries, B.Poitevin, "Modification of 4 MHz N.M.R. water proton relaxation times in very high diluted aqueous solutions", in *Signal and Images*, M.Bastide Ed,Kluwer Academic Publisher, Dordrecht, in press.

[3] J.Schulte, P.C.Endler, "Outline of experimental physical methods to investigate specific structures of ultra high diluted solvents", pp 99-104, in *Ultra High Dilution, Physiology and Physics,* Endler and Schulte Eds, Kluwer Academic Publisher, Dordrecht, 1994.

[4] J.Schulte, "Conservation of structures in aqueous ultra high dilutions", pp 105-115, in *Ultra High Dilution, Physiology and Physics,* Endler and Schulte Eds, Kluwer Academic Publisher, Dordrecht, 1994.

[5] E. Del Giudice, "Is the memory of water a physical impossibility", pp 117-119,pp 5-19, in *Ultra High Dilution, Physiology and Physics,* Endler and Schulte Eds, Kluwer Academic Publisher, Dordrecht, 1994.

[6] G.S.Agnastostatos, "Small water clusters (clathrates) in the preparation process of homeopathy", pp 121-128, pp 5-19, in *Ultra High Dilution, Physiology and Physics,* Endler and Schulte Eds, Kluwer Academic Publisher, Dordrecht, 1994.

[7] P.C.Endler, W.Pongratz, C.W.Smith, J.Schulte, "Non-molecular information transfer from thyroxine to frogs with regard to homeopathic toxicology", *Vet.Human Tox.*, 37, pp 259-260, 1995.

[8] R.Van Wijk and F.A.C.Wiegant, "Physiological effects of homeopathic medicines in closed phials; a critical evaluation", pp 81-95, in *Ultra High Dilution, Physiology and Physics,* Endler and Schulte Eds, Kluwer Academic Publisher, Dordrecht, 1994.

[9] P.C.Endler, W.Pongratz, C.W.Smith, J.Schulte, F.Senekowitsch, M.Citro, "Non molecular information transfer from thyroxine to frogs", in *Signal and Images*, M.Bastide Ed, Kluwer Academic Publisher, Dordrecht, in press.

[10] L.Hadji, B.Arnoux and J.Benveniste, "Effect of dilute histamine on coronary flow of guinea-pig isolated heart. Inhibition by a magnetic field". *FASEB*, n°7040, 1992.

[11] M.Bastide, A.Lagache, "A new paradigm applied to high dilution effects on the living body", see the corresponding chapter in this book.

[12] O.Andersen, K.B.Doving, "Gonadotropin releasing hormone, a novel olfactory stimulant in fish", *Neuroreport,* 2, pp 458-460, 1991.

[13] S.Pavel, D.Psatta, R.Goldstein, "Slow-wave sleep induced in cats by extremely small amounts of synthetic and pineal vasotocin injected into the third ventricle of the brain", *Brain Res. Bull.*, 2, pp 251-254, 1977.

[14] J.Markovac, G.W.Goldstein "Picomolar concentrations of lead stimulate brain protein kinase C", *Nature*, 334, pp 71-73, 1988.

[15] J. Leung-Tack, J.Martinez, J.L.Sansot, Y.Manuel, A.Coll, "Inhibition of phagocyte functions by a synthetic peptide lys-pro-pro-arg (postin)", *Protides Biol.Fluids Proc.Colloq.*, 34, pp 205-208, 1986.

[16] F.Boudard, M.Bastide, "Inhibition of mouse T-cell proliferation by CGRP and VIP: effects of these neuropeptides on IL-2 production and cAMP synthesis", *J.Neurosc.Res.*, 29, pp 29-41, 1991.

[17] T.Tsuchitani, J.Zighelboim, J.Berek, B.Bonavida, "Potentiation of cytotoxicity against human ovarian cell-lines with combinations of subtoxic concentrations of tumor necrosis factor and adrianamycin or cisplatinum", J.Cell.Pharmacol., 2, pp 1-11, 1991.

[18] H.Morimoto, J.S.Safrit, B.Bonvida, "Synergistic effect of tumor necrosis factor α and diphteria toxin-mediated cytotoxicity in sensitive and resistant human ovarian tumor cell lines", J.Immunol, 147, pp 2609-2616, 1991.

[19] J.T.Safrit, B.Bonavida, "Hierarchy of in vitro sensitivity and resistance of tumor cells to cytotoxic effector cells, cytokines, drugs and toxins", Cancer Immunol. Immunother., 8 pages, Springer-Verlag Publisher, Heidelberg, 1992.

[20] P.Bellavite, S.Chirumbolo, G.Lippi, G.Andrioli, L.Bonazzi, L.Ferro, "Dual effcts of formylpeptides on the adhesion of endotoxin-primed human neutrophils", Cell.Biochem.Funct, 11, pp 231-239, 1993.

[21] P.Bellavite, S.Chirumbolo, C.Santonastaso, D.Biasi, S.Lussignoli, G.Andrioli, "Dose-dependence of the various functional responses of neutrophils to formylpeptides", in *Signal and Images*, M.Bastide Ed, Kluwer Academic Publisher, Dordrecht, in press.

[22] C.M.Southam, J.Erlich, "Effects of extracts of western red-cedar heartwood on certain wood-decaying fungi in culture", *Phytopathology*, 33, pp 515-524, 1948.

[23] A.R.D.Stebbing, "Hormesis- Stimulation of colony growth in Campanularia flexuosa, (hydrozoa) by copper, cadmium and other toxicants", *Aquatic Tox*., 1, pp 227-238, 1981.

[24] M.Oberbaum, J.Cambar, "Hormesis: dose-dependent reverse effects of low and very low doses", pp 5-18, in*Ultra High Dilution, Physiology and Physics,* Endler and Schulte Eds, Kluwer Academic Publisher, Dordrecht, 1994.

[25] H.Wagner, B.Kreher, K.Jurcic, "In vitro stimulation of human granulocytes and lymphocytes by pico- and fentogram quantities of cytostatic agents", *Arzneim.Forsch./Drug Res*., 38, pp 273-275, 1988.

[26] H.Schultz, "Uber die theorie der arzneimittelwirkung", *Virchows Archiv*, 108, pp 423-434, 1877.

[27] S.Arinaga, M.Adashi, N.Karimine, H.Inoue, T.Asoh, H.Ueo, T.Akiyoshi, "Enhanced induction of lymphokine-activated killer activity follwing a single dose of cisplatin in cancer patients", *Int.J.Immunpharmac*., 16, pp 519-524, 1994.

[28] P.Weis, J.S.Weis, "Cadmium acclimation and hormesis in Fundulus heteroclitus during fin regeneration", *Environ.Res*., 39, pp 356-363, 1986.

[29] R.van Wijk, H.Ooms, F.A.C. Wiegant, J.E.M.Souren, J.H.Ovelgönne, J.M.van Aken, A.W.J.M.Bol, "A molecular basis for understanding the benefits from subharmful doses of toxicants; an experimental approach to the concepts of hormesis and the homeopathic similia law", *Environ.Manag. Health,* 5, pp13-25, 1994.

[30] R.Van Wijk, M.Welters, J.A.Souren, H.Ovelgonne, F.A.Wiegant. "Serum-stimulated cell cycle progression and stress protein synthesis in C3H10T1/2 fibroblasts treated with sodium arsenite", *J.Cell.Physiology*, 155, pp 265-272, 1993.

[31] R.van Wijk, F.A.C. Wiegant, in *Cultured mammalian cells in homeopathy research- the similia principle in self recovery*, University Utrecht Publisher, 1994.

[32] A.Conforti, S.Lussignoli, S.Bertrani, R.Ortolani, G.Verlato, P.Bellavite, "Intraperitoneal administration of adjuvant inhibits the development of adjuvant arthritis in rats", Int.J.Immunopathol.Immunopharmacol., 8, pp 113-121, 1995.

[33] P.J.Neafsey, "Longevity hormesis, a review", *Mechanims Ageing Develop*, 54, pp 1-13, 1990.

[34] J.C.Cal, F.Larue, J.Guillemain, J.Cambar, "Chronobiological approach of protective effects of Mercurius corrosivus against mercury-induced nephrotoxicity", *Ann. Rev. Chrnonopharmacol*., 3, pp 99 102, 1986.

[35] A.Delbancut, "Contribution à l'étude des effets de hautes dilutions de métaux vis-à-vis de la cytotoxicité du Cadmium sur des cultures de cellules tubulaires rénales", *Thèse Université Bordeaux II, France*, Juillet 1994.

[36] C. Taddei Ferreti and A Cotugno, "Treatment of the teratogenicity induced in mice by caffeine or adenine", *Progr.Biochem.Biotechnol*., 3, pp.*in press*, 1995.

[37] C.Doutremepuich, O. De Seze, D.Le Roy, M.C.Lalanne, M.C.Anne, "Aspirin at very ultra low dosage in healthy volunteers effects on bleeding time, platelet aggregation and coagulation", *Haemostasis*, 20, pp 99-105, 1990.

[38] C.Doutremepuich, O.Aguejouf, D.Pintigny, M.N.Sertillanges and O. De Seze, "Thrombogenic properties of ultra-low-doses of acetylsalicylic acid in a vessel model of laser-induced thrombus formation", *Thrombosis Reseach*, 76, pp 225-229, 1994.

[39] W.Pongratz and P.C.Endler, " Reappraisal of a classical botanical experiment in ultra high dilution research. Energetic coupling in a wheat model", pp 19-26, in *Ultra High Dilution, Physiology and Physics,* Endler and Schulte Eds, Kluwer Academic Publisher, Dordrecht, 1994.
[40] J.A.Hoffman, J.L.Dimarc, P.Bulet, ,"Les peptides antibactériens inductibles des insectes", Med.Sci., 8, pp 432-439, 1992.
[41] S.Metalnikoff, "Immunité naturelle ou acquise des chenilles de Galleria mellonella, C.R.Soc.Biol., 83, pp 278-280, 1920.
[42] G.Bateson, *Steps to an ecology of mind*, Chandler Publisher, New-York, 1972.
[43] M.Bastide, F.Boudard, "High dilutions as a tool of immunomodulation", see the corresponding chapter in this book.
[44] M.Bastide, "Immunological examples on ultra high dilution research", pp 27-33, in *Ultra High Dilution, Physiology and Physics,* Endler and Schulte Eds, Kluwer Academic Publisher, Dordrecht, 1994.
[45] M.Bastide, M.Doucet-Jaboeuf, V.Daurat, " Activity and chronopharmacology of very low doses of physiological immune inducers",*Immunol. Today,* **6**, pp 234-235, 1985.
[46] B.J.Youbicier-Simo, F.Boudard., M.Mekaouche, M.Bastide., J.D.Baylé. "Effects of embryonic bursectomy and *in ovo* administration of highly diluted bursin on adrenocorticotropic and immune response of chickens", *Int.J.Immunotherapy,* 9, pp 169-180, 1993.
[47] L.Hadji, B.Arnoux, J.Benveniste, "Effect of dilute histamine on coronary flow of guinea pig isolated heart. Inhibition by a magnetic field", FASEB J., 5, pp 1583, 1991.
[48] J.Benveniste, B.Arnoux and L.Hadji, " Highly dilute antigen increases coronary flow of isolated heart from immunized guinea-pigs", *FASEB* n° 3900, 1992.
[49] M.H.Litime, J.Afssa and J.Benveniste,"Antigen signalling at high dilution", *FASEB*, n° 3488, 1992.
[50] P.C.Endler, W.Pongratz, R.Van Wijk, F.A.C.Wiegant, K.Waltl, M.Gehrer, H.Hilgers, "A zoological example on ultra high dilution research. Energetic coupling between the dilution and the organism in a model of amphibia", pp 39-68, in *Ultra High Dilution, Physiology and Physics,* Endler and Schulte Eds, Kluwer Academic Publisher, Dordrecht, 1994.
[51] P.C.Endler, Corresponding chapter in this book.
[52] M.Oberbaum, R.Markovits, Z.Weisman, A.Kalinkevits, Z.Bentwich," Wound healing by Homeopathic Silica Dilutions in Mice", *Harefuah*, 123, pp 79-82, 1992.
[53] M.Oberbaum, see the corresponding chapter in this book.