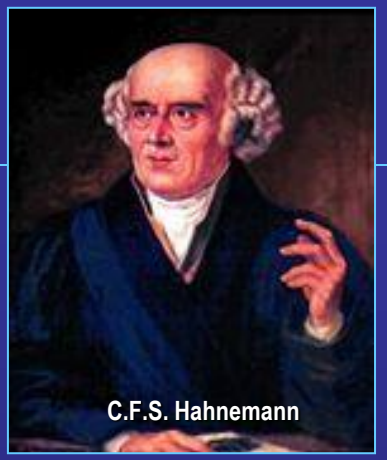


The scientific foundations of homeopathy

Wien 29 oct 2014

Prof. Paolo Bellavite - Università di Verona

Is there a bridge?

British Homœopathic Journal
October 1989. Vol. 78. pp. 230–236

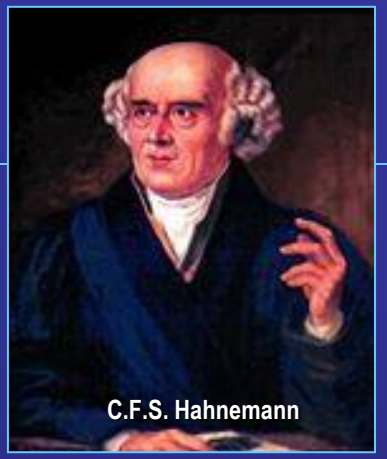
Is there a bridge between homœopathy and conventional medicine?

Blackie Memorial Lecture

PROFESSOR PAUL TURNER

Homœopathy and conventional medicine are, therefore, to be seen as expressions of that reality which is the basis, the foundation, of both. It is by experimentally tunnelling down together into that reality, moving towards each other through that reality, that we will eventually understand the true nature of disorders that we all seek to treat, and the mechanisms of action of our various forms of therapy.

The scientific foundations of homeopathy



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1. Introduction: the wide field of homeopathic science
2. The «simile» as inversion of effects
   - The dose-response curves (Arndt-Schulz, Hormesis)
   - The state of the treated system (Wilder rule, paradoxical pharmacology)
3. How small the dose?

«Scientific» oppositions to homeopathy

nature Vol 446|22 March 2007

SPECIAL REPORT

Degrees in homeopathy slated as unscientific

Alternative therapies are now a degree subject at some British universities. But do they deserve these credentials? **Jim Giles** reports.

As debate rages in the United States over whether intelligent design should be taught in science classes, another topic that many researchers see as a pseudoscience is claiming scientific status within the British education system.

Over the past decade, several British universities have started offering bachelor of science (BSc) degrees in alternative medicine, including six that offer BSc degrees in homeopathy, a therapy in which the active ingredient is diluted so much that the dose given to the patient often does not contain even a single molecule of it. Some scientists are increasingly concerned that such courses give homeopathy and homeopaths undeserved scientific credibility, and they are campaigning to get the label removed (see Commentary, page 373).

Many scientists and advocates of evidence-based medicine feel that giving homeopathy scientific status is unjustified. Aside from the fact that there is no known mechanism by which this treatment could work, they argue that the evidence against it is conclusive. Of the many rigorous systematic reviews conducted in the past decade, only a handful have produced

Pharmacologist David Colquhoun of University College London has had the same problem, and is now using freedom-of-information legislation to get access to course materials after having numerous requests refused. The University of Central Lancashire and the University of Salford both declined requests to talk to *Nature* or share details of their homeopathy degrees.

One university that is willing to discuss its teaching is the University of Westminster in London. Brian Isbell, head of Westminster's department of complementary therapies, defends the BSc description, arguing that as with all of the university's complementary therapy degrees, students also have to study the health-sciences model of disease, so that they can "work safely and effectively within the healthcare system". Students are required to do research and produce critiques of the literature. Reading lists include papers from sources such as *Homeopathy*, a journal published by the Faculty of Homeopathy, a members' association for professional homeopaths based in Luton. But the lists also include recent studies that are critical of homeopathy and conventional guides

Homeopathic medicine is big business, but giving it the status of a science degree is controversial.

«Scientific» oppositions to homeopathy

bioethics

Bioethics ISSN 0269-9702 (print); 1467-8519 (online)
Volume 26 Number 9 2012 pp 508–512

doi:10.1111/j.1467-8519.2011.01956.x

RESPONSE

HOMEOPATHY IS UNSCIENTIFIC AND UNETHICAL

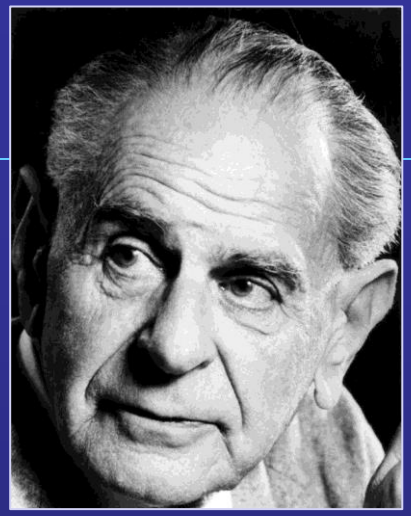
KEVIN SMITH

Keywords
homeopathy,
alternative medicine,
complementary medicine,
CAM

ABSTRACT

In opposition to the premises of Against Homeopathy – a Utilitarian Perspective, all four respondents base their objections on the central claims that homeopathy is in fact scientifically plausible and is supported by empirical evidence. Despite ethical aspects forming the main thrust of Against Homeopathy, the respondents' focus on scientific aspects represents sound strategy, since the ethical case against homeopathy would be weakened concomitant with the extent to which any plausibility for homeopathy could be demonstrated. The trouble here is that the respondents are attempting to perpetuate a sterile debate. The notion that homeopathic

IS HOMEOPATHY A SCIENCE?

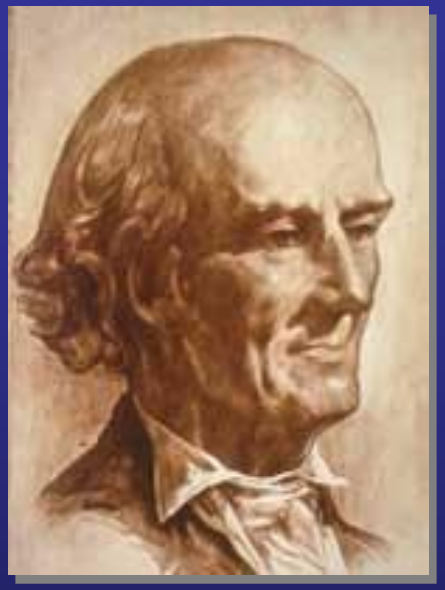


- What is science?
- What is scientific?

"We must not look upon science as a "body of knowledge", but rather as a system of hypotheses, with which we work as long as they stand up to tests…"

- Karl R. Popper (1902-1994), *The Logic of Scientific Discovery*

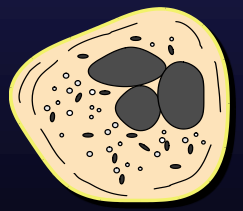
TESTING HOMEOPATHY MAIN HYPOTHESIS IS A SCIENTIFIC TOPIC



C.F.S. Hahnemann
(1755-1843)

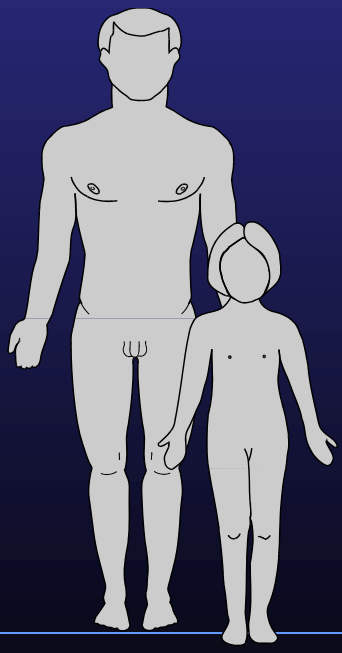
"The majority of substances have more than one action;
the first is a direct action, which gradually changes into the second,
which I call its indirect secondary action.
The second is generally the opposite of the first"

C.F.S. Hahnemann, 1796

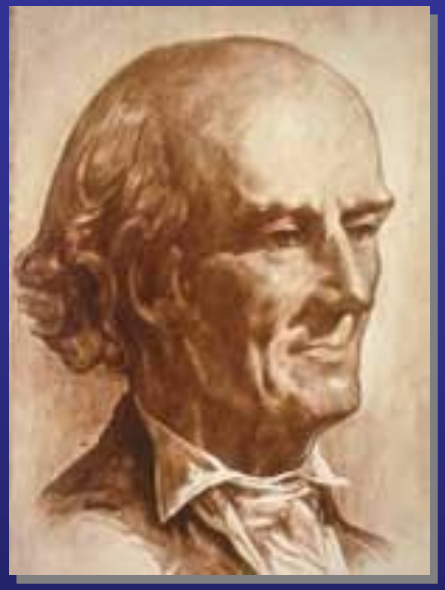


TRUE FALSE

SCIENTIFIC RESEARCH



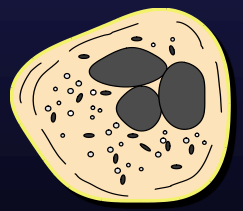
TESTING HOMEOPATHY MAIN HYPOTHESIS IS A SCIENTIFIC TOPIC



C.F.S. Hahnemann
(1755-1843)

"A medicine whose selection has been accurately homoeopathic must be all the more salutary the more its dose is reduced to the degree of minuteness appropriate for a gentle remedial effect..."

C.F.S. Hahnemann, 1810
Organon, par. 277



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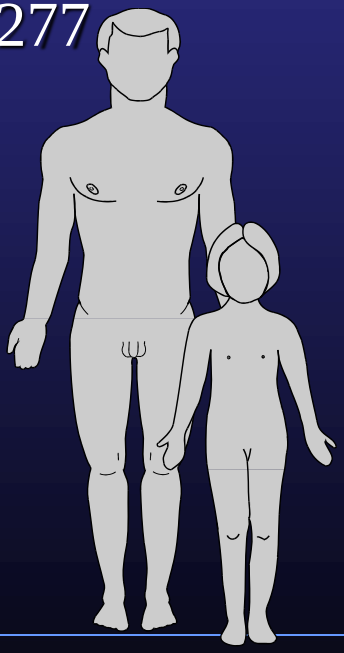
SCIENTIFIC RESEARCH



Scientific investigation of the main homeopathic principles

PHASE 1. Proving
(HEALTHY SUBJECTS)

- Knowledge of "pathogenetic" symptoms
- Is it a placebo response?

INDIVIDUAL CARE, HOLISTIC APPROACH

PHASES 2-4 and
OBSERVATIONAL
(SICK SUBJECTS)

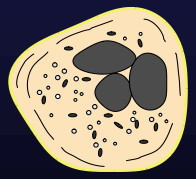
- **Is homeopathy effective?**
- Is the medicine a placebo?
- Adverse effects?
- Is it equivalent to allopathy?
- Is it cost-effective?

CLINICAL RESEARCH

PRINCIPLE OF "SIMILARITY"

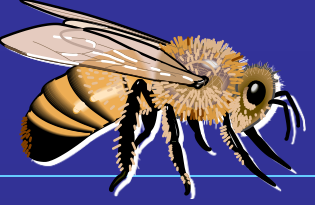
DILUTION AND DYNAMIZATION

BASIC RESEARCH



- In vivo (animal models)
- In vitro (cellular systems)
- Biophysics ("water memory")

- How does it work?
- Targets (cells/organs/psyche)
- Components and quality control



Developments of experimental studies on APIS M.

1975--1990
- High dilutions (7C-9C) of *Apis mellifica*, which are currently used in homeopathy to treat skin manifestations with edema, erythema and pruritus) have a protective and curative effect on about 50% of X-ray induced erythema in albino guinea pig [Bastde1975, Bildet 1990]

1993
- Dilutions of up to 30D of *Apis mellifica* (and *Histamin)* reduce rat paw edema induced by the injection of inflammatory doses of histamine. (Conforti, Bellavite et al.,1993).

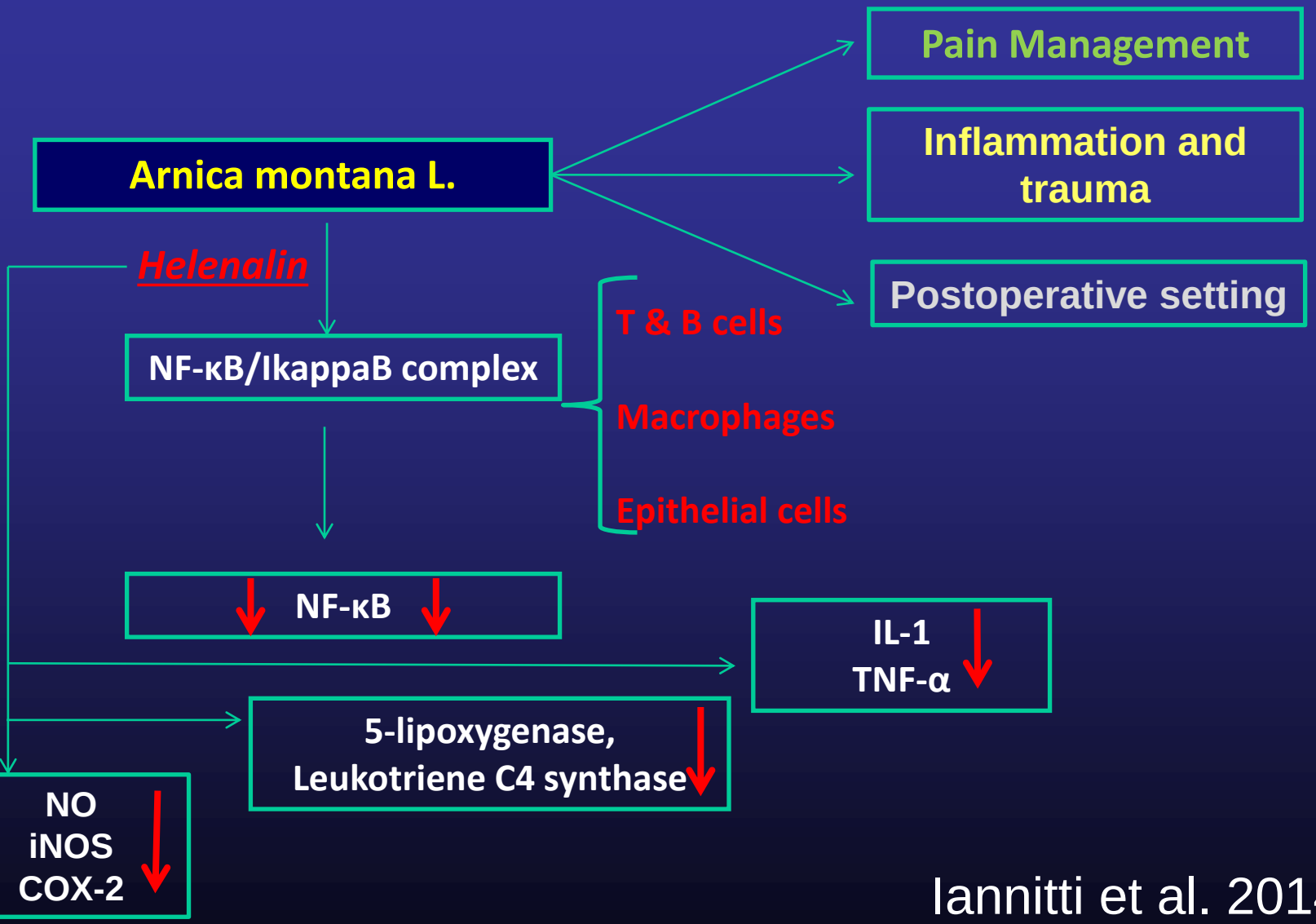
2004
- We confirmed a small regulating effect of *Apis mellifica* (4 D, oral drops) in the carrageenan-induced edema in rats [Conforti et al., 2004) in open trial

2014
- Bigagli and coworkers (2014) showed with microarray techniques that *Apis mellifica* TM modifies expression of hundreds of genes in human prostate epithelial cells; dynamized dilutions (3C, 5C and 7C) still exert significant effects on genes involved in inflammation and oxidative stress

Arnica montana actions

Ref.	Type of study	Active compounds	Treatment	Effects	Mechanism of action
M.˘Sutovská et al. 2014	In vivo using rats	Hydroalcholic exctract of dried flowers	Allopatic, but not dose dependent (lowest dose of 50 mg/kg more effective)	bronchodilatory effect of AM on tracheal smooth muscle causes the antitussive effect	Not investigated
Daniel PetinattiPavarini et al. 2013	In vivo using rat peritoneal macrophages cultures. In vitro for cytokines test	orto-acetoxy-bisabolol	Allopathic, at low doses (3-10 ug/ml)	Anti-inflammatory and anti-nociceptive	significantly reduction in IL-1β and TNF-α levels in animals stimulated with LPS
R. A. de Camargo et al. 2013	In vivo using rats	Hydroalcholic exctract of dried flowers	6cH, 12cH, 30cH 21 days	30cH inhibition of lipid peroxidation of mitochondrial membranes; decrease in O2 consumption	not investigated
T. Iannitti et al. 2014	Clinical, Post-Surgical	Pomata and oral administration of homeopathic remedies	Allopathic and homeopathic	anti-inflammatory and anti-nociceptive properties in the treatment of osteoarthritis, postoperative edema, and ecchymosis	not investigated
Guido Lyß et al. 1998	In vitro T-cells	Helenaline, sesquiterpene lactone isolated from Arnica Montana	10 µM Helenalin	Anti inflammatory	Helenalin selectively alkylates the sulfhydryl groups of p65 subunit of NF-kB
Lim et al., 2012	human ovarian cancer cell line, colon carcinoma cancer cell line, breast adenocarcinoma cancer cell line	Helenaline, sesquiterpene lactone isolated from Arnica Montana	1-10 µM	increase in cell death via G1 arrest, apoptosis and autophagy, with increased levels of caspase cleavage.	Helenalin treatment reduced the level of NF-κB p65 (gene suppression) and this increases caspase cleaveage
Craciunescu et al., 2012	mouse fibroblast-like NCTC cell line	Hydroalcholic exctract of dried flowers	10–500 mg/L	antioxidant and cytoprotective activities	Not investigated
Khuda Bukhsh et al.,2012	E.coli	Hydroalcholic exctract of dried flowers	30 ch	Diminished cellular stress (measured with ROS generation, SOD, Catalase and glutathione)	Increased express of DNA repair genes (uvrA,B,C)
Ghasemali S et al., 2013	T47D brest cancer cell line	β-Cyclodextrin-helenalin	allopathic	cytotoxic effects, anti-cancer	down-regulation of telomerase expression genes

Arnica montana actions



Iannitti et al. 2014

Phosphorus «PATHOGENESIS»

- **Toxicity (Merck Manual)**
- Phosphorus is hazardous to all domestic animals and is locally corrosive and hepatotoxic when absorbed.
- The onset of signs of poisoning is sudden. Early signs include vomiting, severe diarrhea (often hemorrhagic), colic, and a garlic-like odor to the breath. Apparent recovery can occur up to 4 days after ingestion, but additional signs of acute liver damage may develop, including hemorrhages, abdominal pain, and icterus.
- Hepatic encephalopathy is followed by convulsions and death.
- Lesions include severe gastroenteritis; fatty liver; multiple hemorrhages; and black, tarry blood that fails to clot. Body tissues and fluids may be phosphorescent, and the gastric contents have a garlic odor. Death is due to hepatic and renal failure.

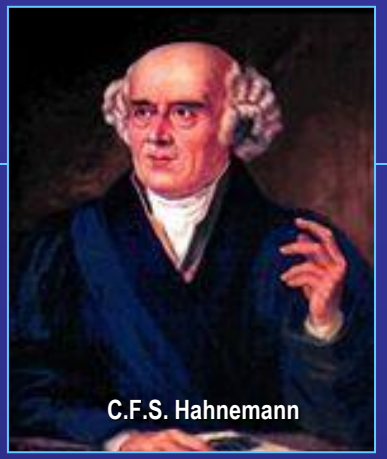
Phosphorus «PATHOGENESIS»

- **Materia Medica (Boericke)**
- Phosphorus irritates, inflames and degenerates mucous membranes, inflames spinal cord and nerves, causing paralysis, destroys bone, especially the lower jaw and tibia; disorganizes the blood, causing fatty degeneration of vessels and every tissue and organ of the body and thus gives rise to hemorrhages, and hematogenous jaundice. Causes yellow atrophy of the liver and sub-acute hepatitis.
- Tall, slender persons, narrow chested, with thin, transparent skin, weakened by loss of animal fluids, with great nervous debility, emaciation, amative tendencies, seem to be under the special influence of Phosphorus. Great susceptibility to external impressions, to light, sound, odors, touch, electrical changes, thunder-storms. SUDDENNESS of symptoms, sudden prostration, sweats, shooting pains, etc. FATTY DEGENERATIONS, cirrhosis, caries, are pathological states often calling for Phosphorus.

Phosphorus RESEARCH

- Protective effect of high dilutions (7c and 15c) of phosphorus on CCl4-induced toxic hepatitis in the rat [Bildet *et al.*, 1975; Bildet *et al.*, 1984a; Bildet *et al.*, 1984b].
- The mortality of rats treated with lethal doses of α-amanitine is significantly slowed by treatment with 15c dilutions of α-amanitine, *Phosphorus*, and rifampicin [Guillemain *et al.*, 1987].
- Protective effect of *Phosphorus* 30c on fibrosis of the liver caused by chronic administration of CCl4 in rats [Palmerini *et al.*, 1993]
- *Phosphorus* and *Magnesia phosphorica* (dilutions greater than 15x), slightly decrease free radical production by human granulocytes [Chirumbolo et al 1993]
- In rats, Phosphorus 12x showed a protective action on the mortality by T. cruzi infection (Chagas disease) [de Almeida et al, 2008]
- Phosphorus high dilutions (15c and 200c) was successfylly used in 2 patients with fulminant hepatic failure from Amanita phalloides poisoning [Frass et al., 2014]

The scientific foundations of homeopathy



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3. How small the dose?

Similia principle

(Principle of Similarity)

when a substance is able to *induce* a series of symptoms in a healthy living system

("pathogenic power")

it would be also able under certain circumstances to *cure* an organism presenting similar symptoms when applied at low doses

("*similia similibus curentur*")

SCIENTIFIC REEVALUATION OF THE HOMEOPATHIC "SIMILE"

GENERAL HYPOTHESIS:

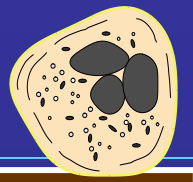
The "therapeutic similarity" in drug action may be fundamentally based on the widespread phenomenon of inversion of biological effects dependent on the following factors:

1. the dose, and/or
2. the physiological state of the receiver

A combination of one or more of these factors and the contribution of complexity science give rise to an complete theory of the homeopathic "simile" effect

Main references in: Bellavite et al .: ECAM Journal 2007 (available online through PubMed-Medline)

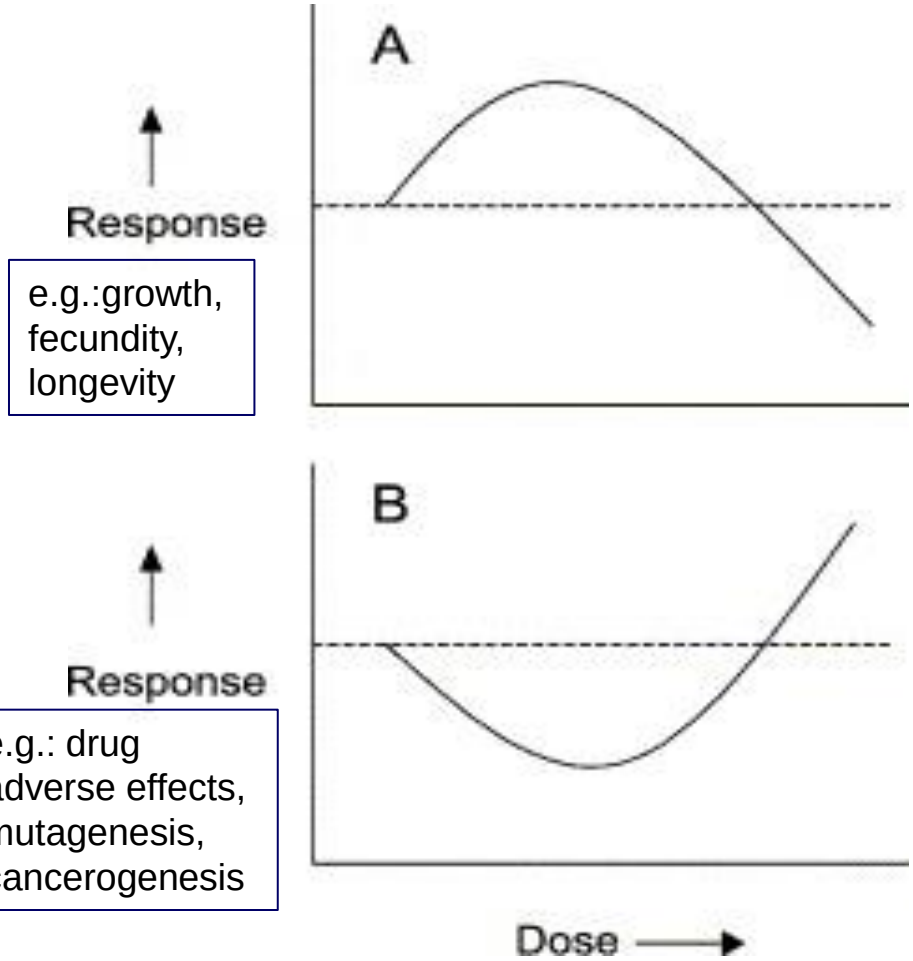
EXAMPLES OF INVERSE EFFECTS WITH HOMEOPATHIC DILUTIONS IN LABORATORY SYSTEMS



System	Agent	"High dose" effect	Homeopathic effect	Ref.
Basophils	Histamine Apis mellifica	Pro-inflammatory agents	Histamine (up to 60x) and Apis mellifica (10c) inhibit basophils	Poitevin 1988, S.Laudy 1991, Belon 1996-2004, Chirumbolo-Bellavite 2009
Rat Guinea pig	Histamine Lung Histamine Apis mellifica	Pro-inflammatory agent	Histamine (30x), Lung histamine (18c) and Apis mellifica (7c/10c) reduce inflammation symptoms	Bastide 1975,Poitevin 1988, Bildet 1990 Conforti and Bellavite1993
Rat Mouse	Arsenic trioxide Arsenicum album	Whole body and liver toxicity	Arsenic trioxide (7c and 17c) and Arsenicum album (30c) protect from intoxication	Lapp 1955; Wurmser 1955; Cazin1987; Cazin 1991; Khuda-Bukhsh 1998-2000
Wheat, hepatoma cells	Arsenic trioxide (As2O3)	Cell toxicity	As2O3 40x, 42x and 45x, stimulate germination and cell vitality	Betti 1997-2000, Wiegant-van Wijk 1998-2011
Rat liver	Phosphorus	Hepatotoxicity	Phosphorus (30x) protects from toxic hepatitis	Bildet 1984, Guillemain 1987 Palmerini 1993 Gomez 1999
Tadpoles	Thyroxine	Increases the rate of metamorposis	High dilutions (up to 30x) inhibit the metamorphosis	Endler 1990-2010, Graunke 2007, Welles 2007, Lingg 2008, Weber 2008, Guedes 2011, Harrer 2013
Human and rat neurons	Gelsemium sempervirens	Excitation and toxicity	Anxiolytic effect (2C-9C), no toxicity, gene down-regulation	Magnani 2010, Venard 2011, Gahlot 2012, Meyer 2013.

HORMESIS

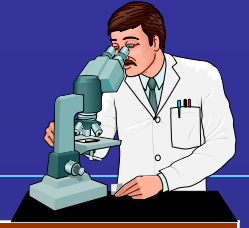
Edward J. Calabrese



CalabreseEJ The Scientist Volume 19 | Issue 3 | 22 | Feb. 14, 2005

Other references in: Bellavite et al .: ECAM Journal 2007 (available online through PubMed-Medline)

EXAMPLES OF INVERSE EFFECTS IN LABORATORY SYSTEMS



System	Agent	First effect	Inverse effect	Ref.
Yeast	Heavy Metals	**Block growth**	**Low doses increase growth**	Schulz 1988 Martius 1923 Stebbing 1982
Fibroblasts Wheat	Arsenite Cadmium	**Cell toxicity**	**Low doses protect from toxicity or stimulate DNA synthesis**	vanWijk 1995 vanWijk 1997 V.Zglinicki 1992 Betti 1997-2000
Neurons	Naloxone	**Antagonizes morphine**	**Low doses enhance the effect of morphine**	Crain 1995
Neurons	β-amyloid	**Toxic for mature cells**	**Promotes growth of young cells**	Yankner 1990
Epithelial cells Tumor cells	Oxidants	**Short-term/high doses decrease viability**	**Long-term/low doses increase viability**	Da Silva 1996 Jenkins 1995
Macrophages	Interfererons Endotoxins	**Activation of resting cells**	**Inhibition of pre-activated cells**	Adams 1992
Platelets	Diclofenac	**Inhibit functions**	**Stimulate platelet adhesion**	Andrioli-Bellavite 1997
Leukocytes	Bacterial peptides	**Stimulate adherence**	**Low doses inhibit adherence**	Bellavite 1993-1997

EXAMPLES OF INVERSE EFFECTS IN ANIMAL SYSTEMS

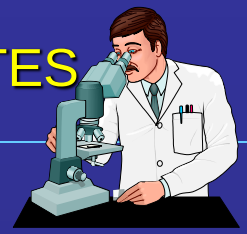
Condition	Agent	First effect	Inverse effect	Ref.
Rat blood	Acetylsalycilic acid	Inhibit platelet aggregation	Very-low doses have thrombogenic activity	Doutremepuich 1994
Dog heart	Ischemia	Causes infarction	Ischemic preconditioning protects from infarction	Cohen 1996
Mouse prostate	Estrogens	Inhibit growth	Low doses promote growth	VomSaal 1997 Gupta 2000
Mouse and rat immune system	Protein antigens	Induce autoimmune disease	Oral administration protects and cure autoimmunity	Miller 1992 Weiner 1997 Wu 1998
Rat arthritis	Naloxone	Hyperalgesia	Low doses have antinociceptive effects	Kayser 1988
Rat liver	Carbon tetrachloride	Toxicity	Low doses protect from liver toxicity	Ugazio 1972 Mehendale 1991 Pound 1993
Rat immune system	Killed mycobacteria	Induce arthritis	Intraperitoneal low-doses cure arthritis	Conforti-Bellavite 1995-2000
Rat nervous system	Beta-amyloid	Decreases neural function	Extremely low dsoses increases neural function	Puzzo et al 2008

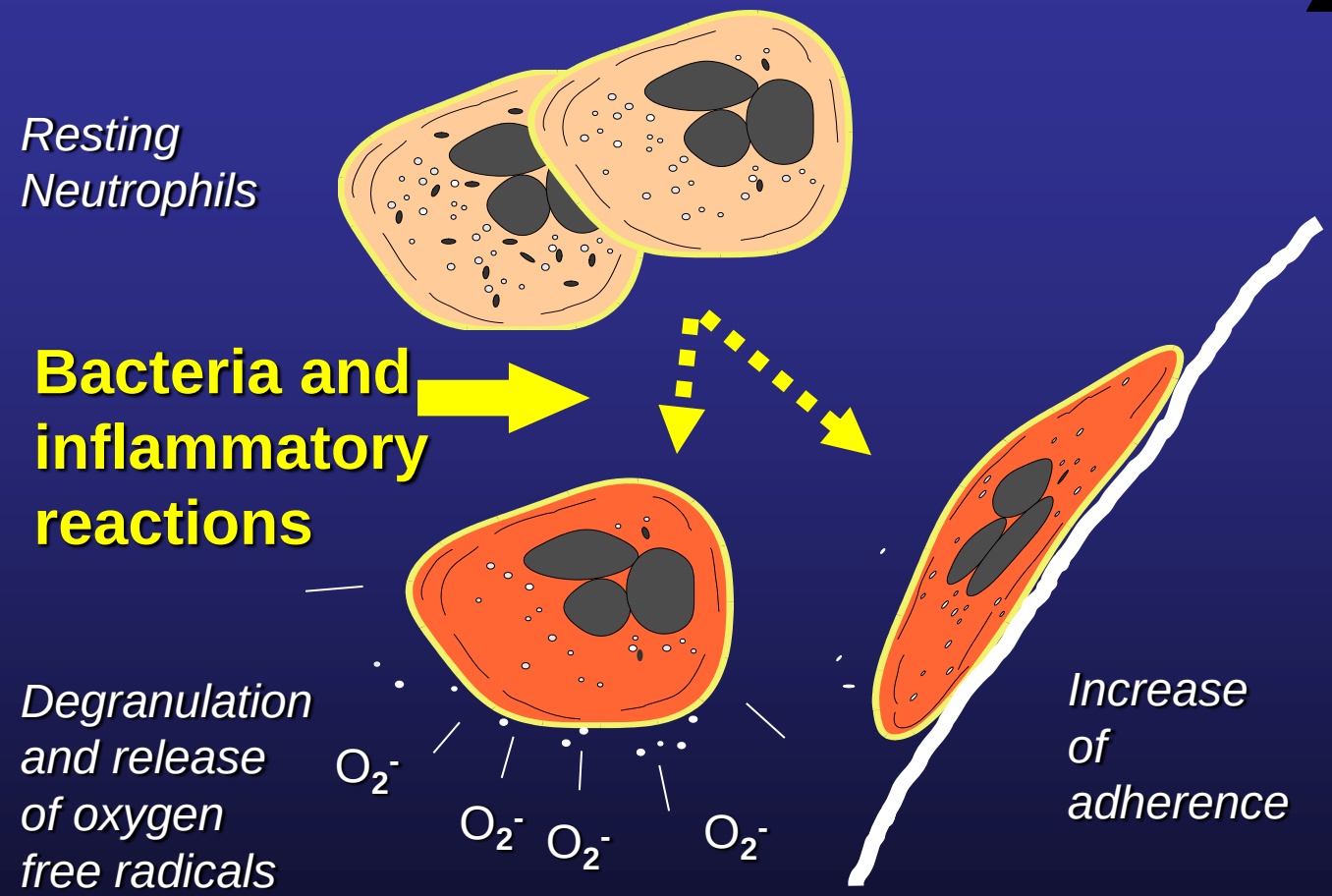
EXAMPLES OF INVERSE EFFECTS IN HUMANS

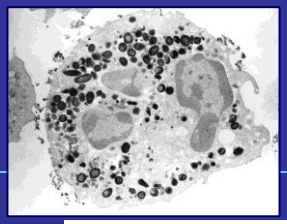
Reviews: P. Bellavite/A. Signorini 1995/2007; M. Teixeira, 1998; D. Eskinazi 1999

Condition	Agent	First effect	Inverse effect	Ref.
Respiratory allergy	**Allergens**	**Cause allergy**	**Very low doses reduce allergy symptoms (also high dilutions 30c)**	Black 1927 Scadding 1986 Malling 1998 Reilly 1987-2000
Bleeding	**Acetylsalycilic acid**	**Increase bleeding time**	**Very low doses (5c=0.000000001 mg) decrease bleeding time**	Doutremepuich 1987-1998
Respiratory disease	**Nitric oxide**	**Toxic inhalant for airways (pollutant)**	**Inhaled low doses cure airways obstruction**	Quinn 1993 Kinsella 1999
Cardiovasc. disease	**Alchohol** **Digitalis**	**High doses are toxic**	**Low doses protect and cure**	Friedman 1986 Davis 1990 Goodman 1990
Rheumatoid arthritis	**Collagen**	**Autoantigen**	**Oral very low doses cure the disease (in some subjects)**	Trentham 1993 Weiner 1997
Cancer	**Ionizing radiations**	**Cancerogenic**	**Epidemiological evidence of protection by low doses**	Goldman 1996
Heart failure	**Beta-blockers**	**Increase output**	**Detrimenal in long-term treatments (“paradoxical pharmacology”)**	Bond 2001

FUNCTIONAL ACTIVATION OF NEUTROPHIL GRANULOCYTES



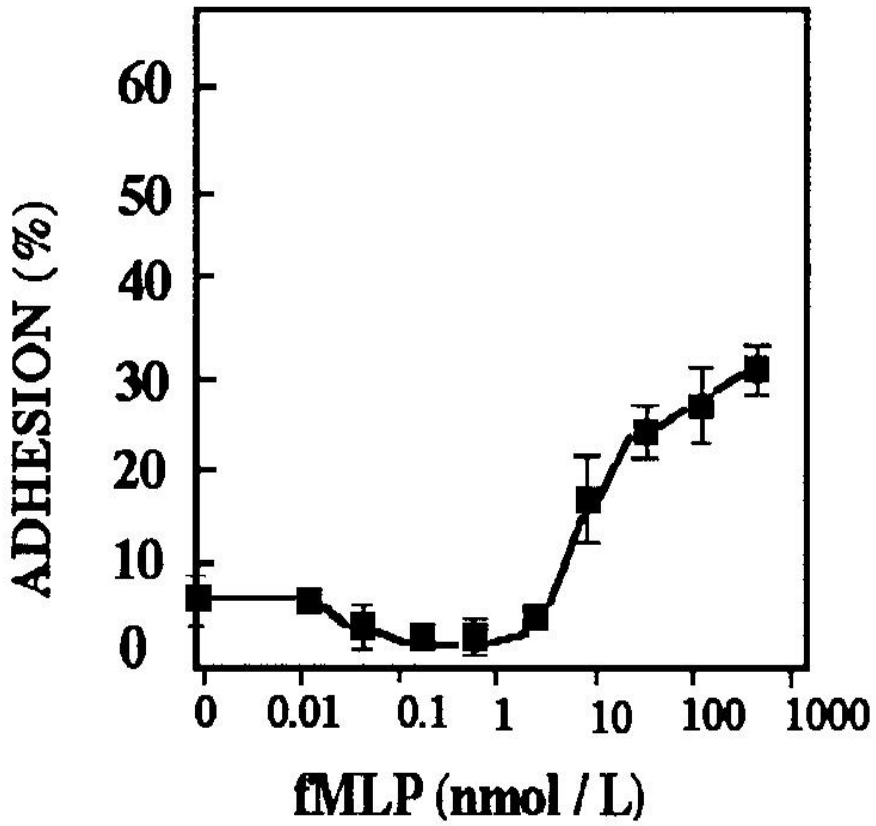




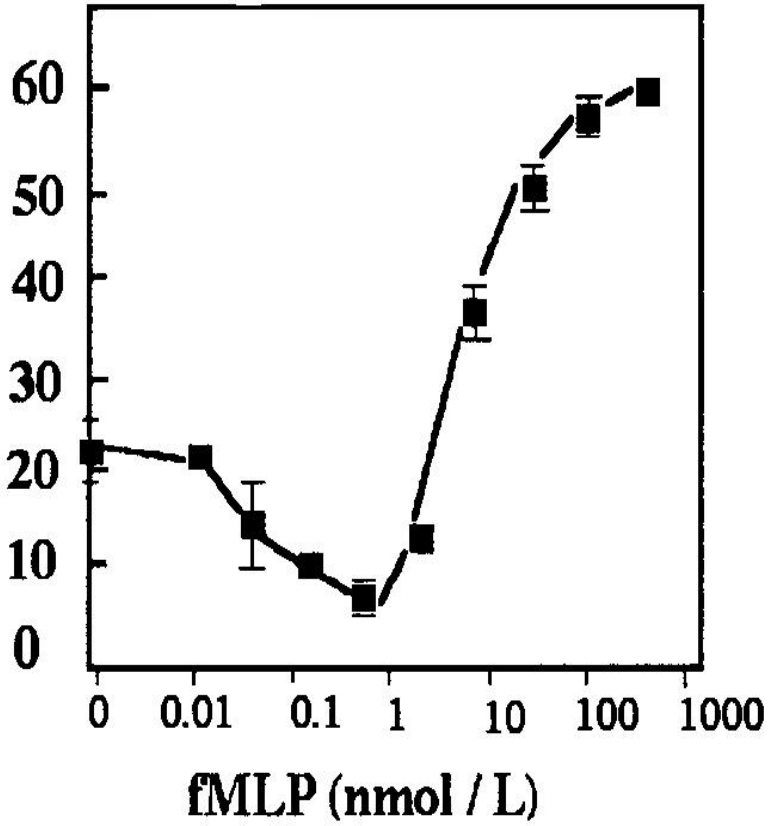
DOSE-DEPENDENCE OF ADHESION CAPABILITY INDUCED BY BACTERIAL PEPTIDES (fMLP) IN HUMAN NEUTROPHILS

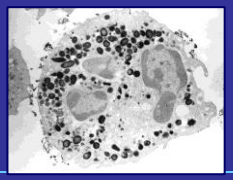
Bellavite et al., 1993-1997

A. Normal cells



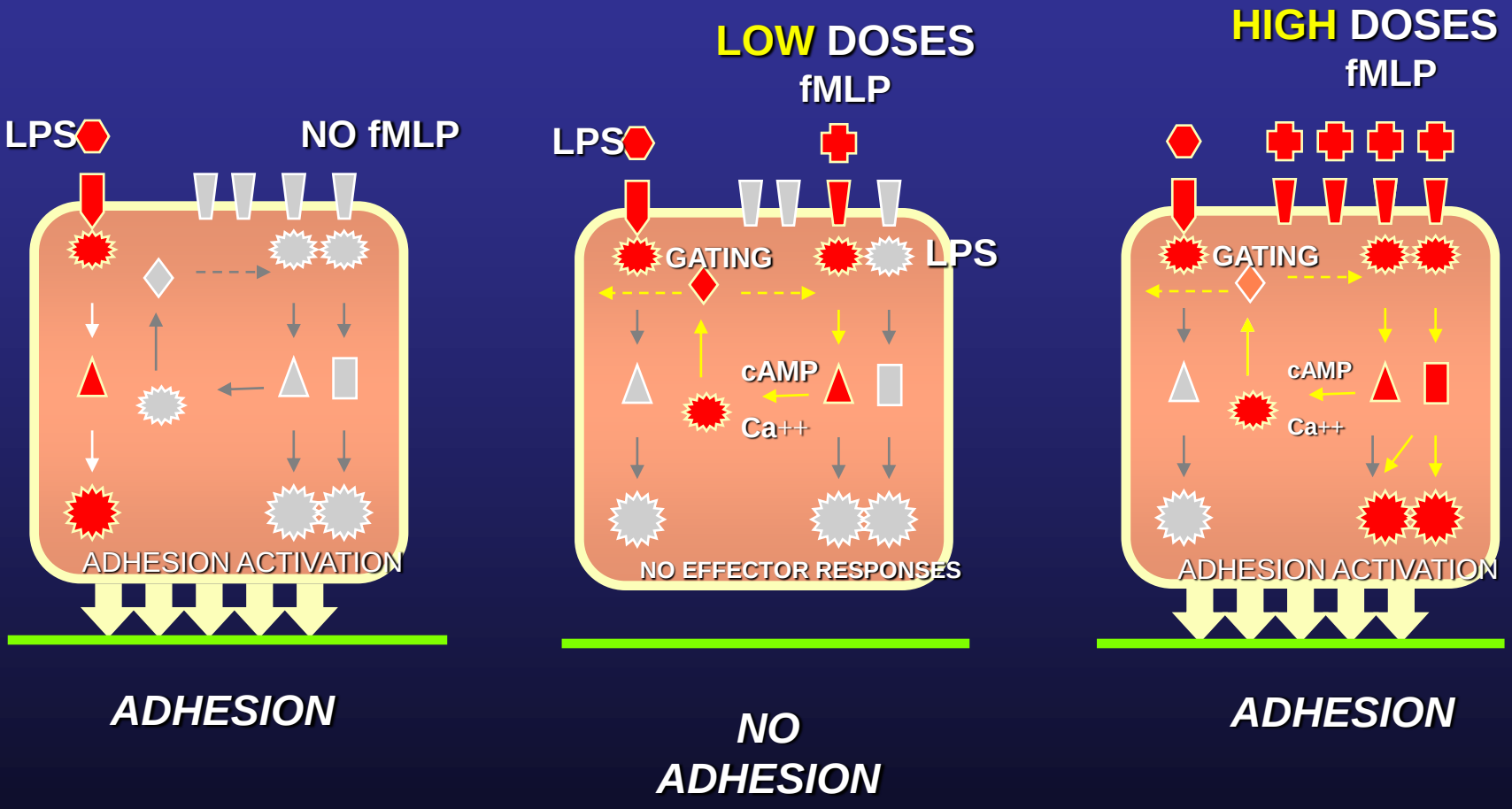
B. Endotoxin pre-treated cells, cells from inflammation site





MODEL OF THE INVERSE EFFECTS OF DIFFERENT DOSES OF fMLP ON LPS-TREATED HUMAN NEUTROPHILS

Bellavite et al. *Br. Hom.J.* 86: 73-85, 1997 – ECAM J 2007



FLAVONOIDS AND INFLAMMATION: THE INTELLIGENCE OF NATURE

International Immunopharmacology 10 (2010) 183–192

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Stimulus-specific regulation of CD63 and CD203c membrane expression in human basophils by the flavonoid quercetin

S. Chirumbolo [a,*], A. Conforti [c], R. Ortolani [b], A. Vella [b], M. Marzotto [a], P. Bellavite [a]

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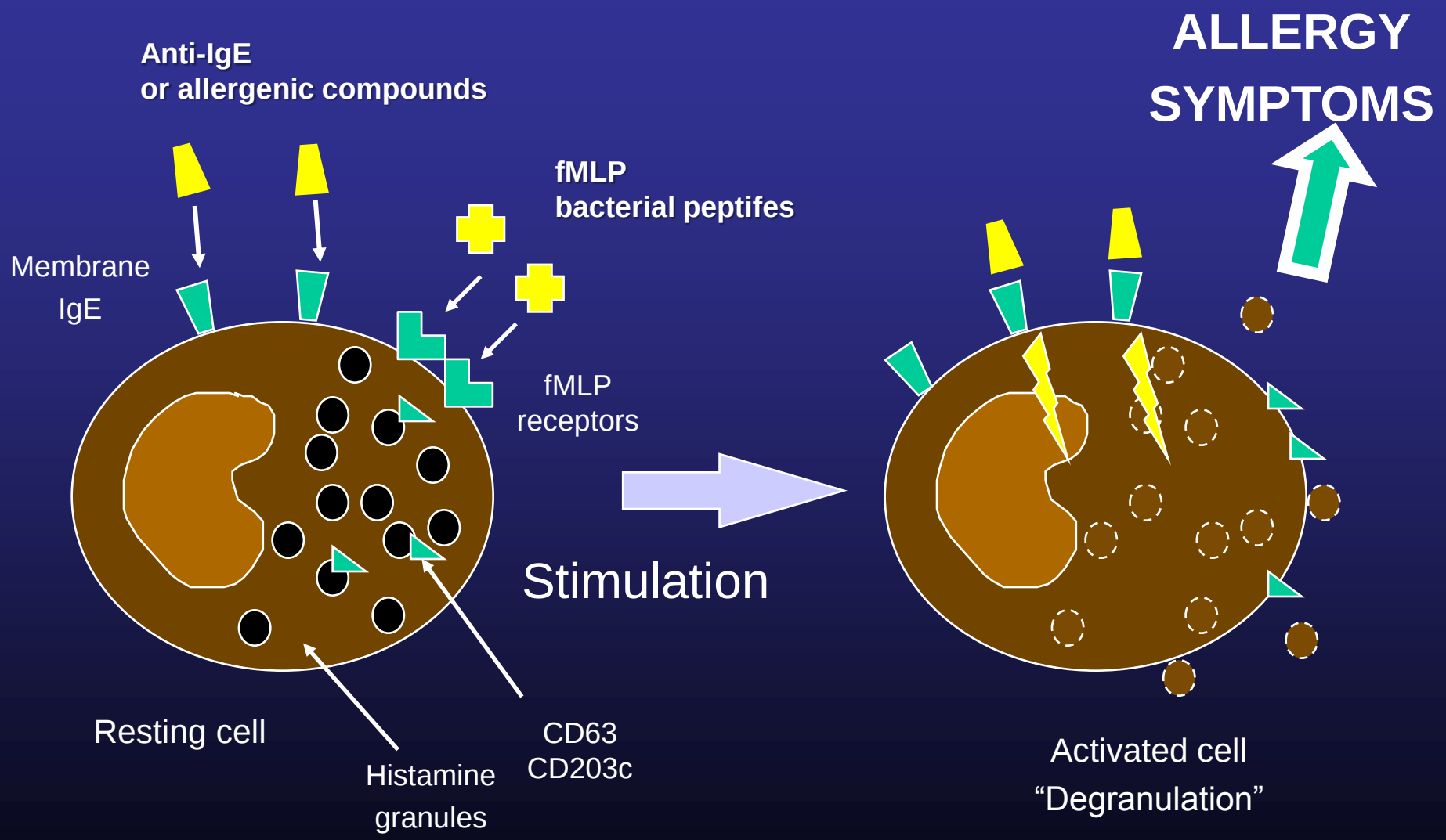
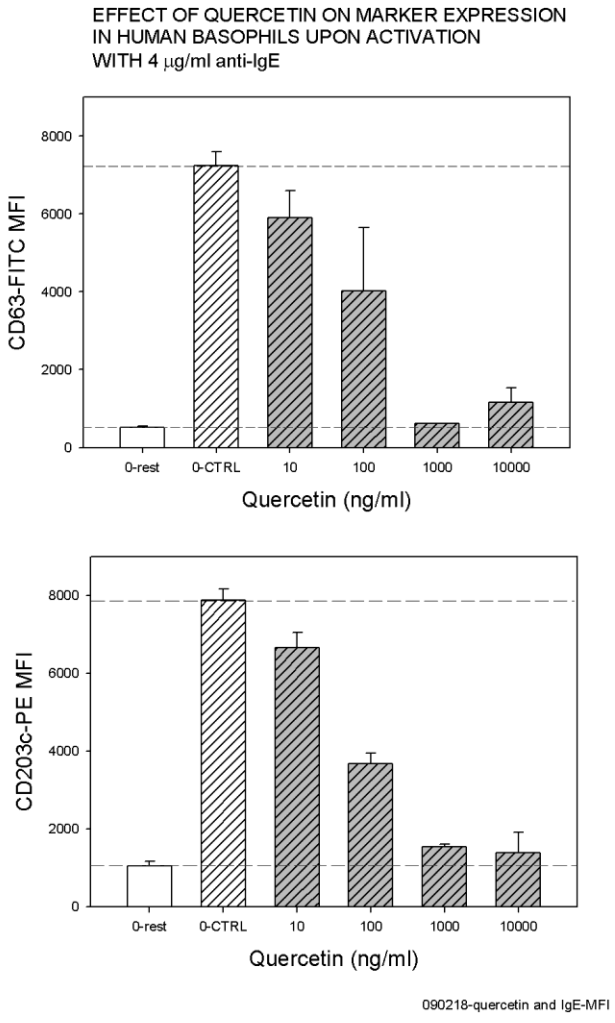
THE MODEL OF BASOPHIL ACTIVATION

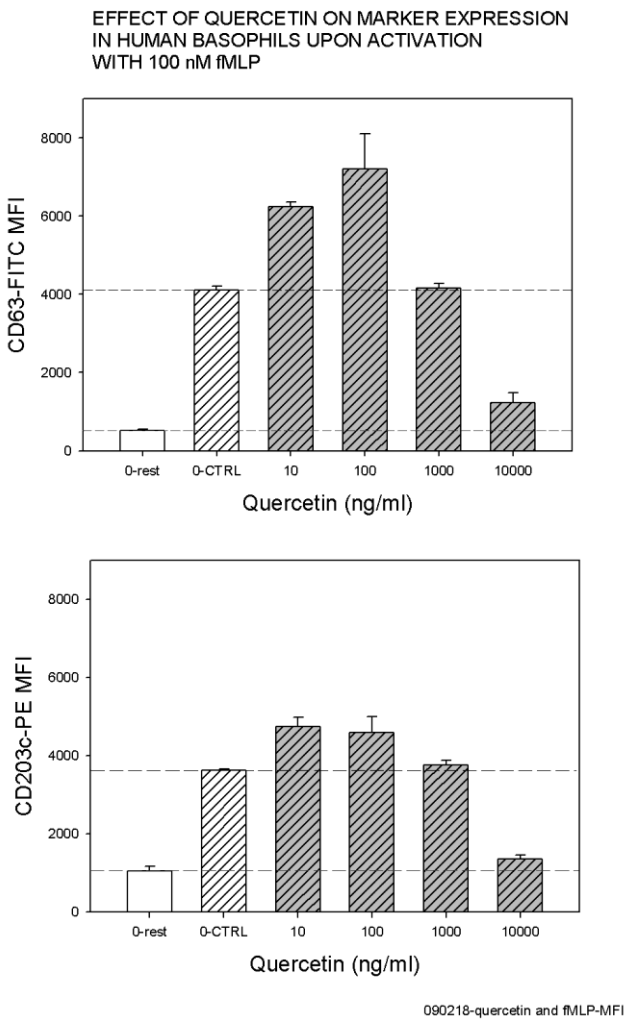


EFFECT OF DIFFERENT DOSES OF QUERCETIN IN HUMAN BASOPHILS

ALLERGY MODEL



INFECTION MODEL



The Physiological state

Inverse effects of drugs on specific target systems can be often observed by changing the *physiological state of the target*.

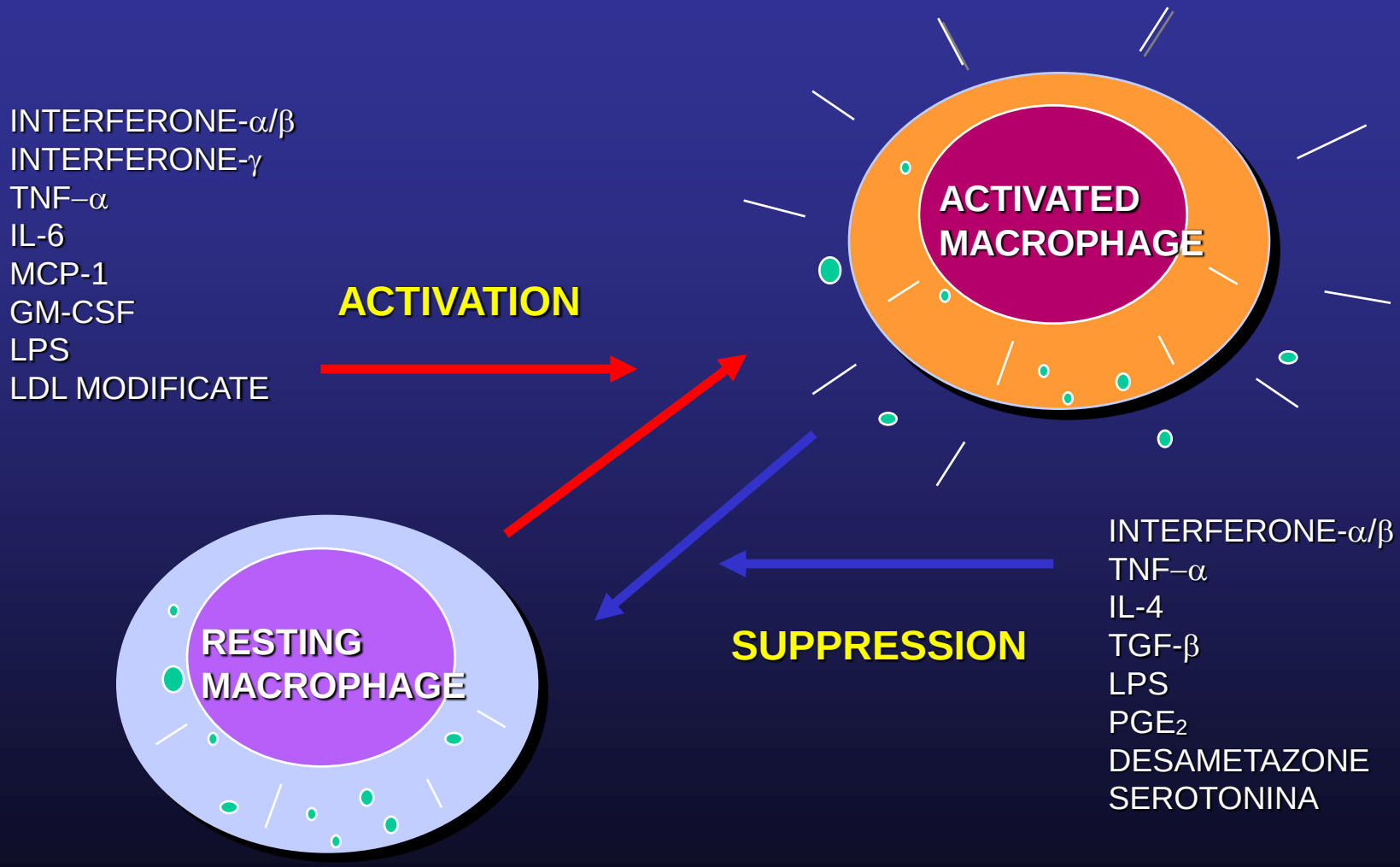
For example, the same or similar compound may be stimulatory on resting cells, inhibitory on stressed or activated cells, may be detrimental in short-term and beneficial in long-term.

This field includes the "Rule of Wilder" and paradoxical pharmacology

Main references in: Bellavite et al .: ECAM Journal 2007 (available online through PubMed-Medline)

INVERSE EFFECTS OF CYTOKINES ON MACROPHAGES (from literature)

(Da lavori citati in “Inflammation”, Raven Press, 1992. Gallin et al. ed.)



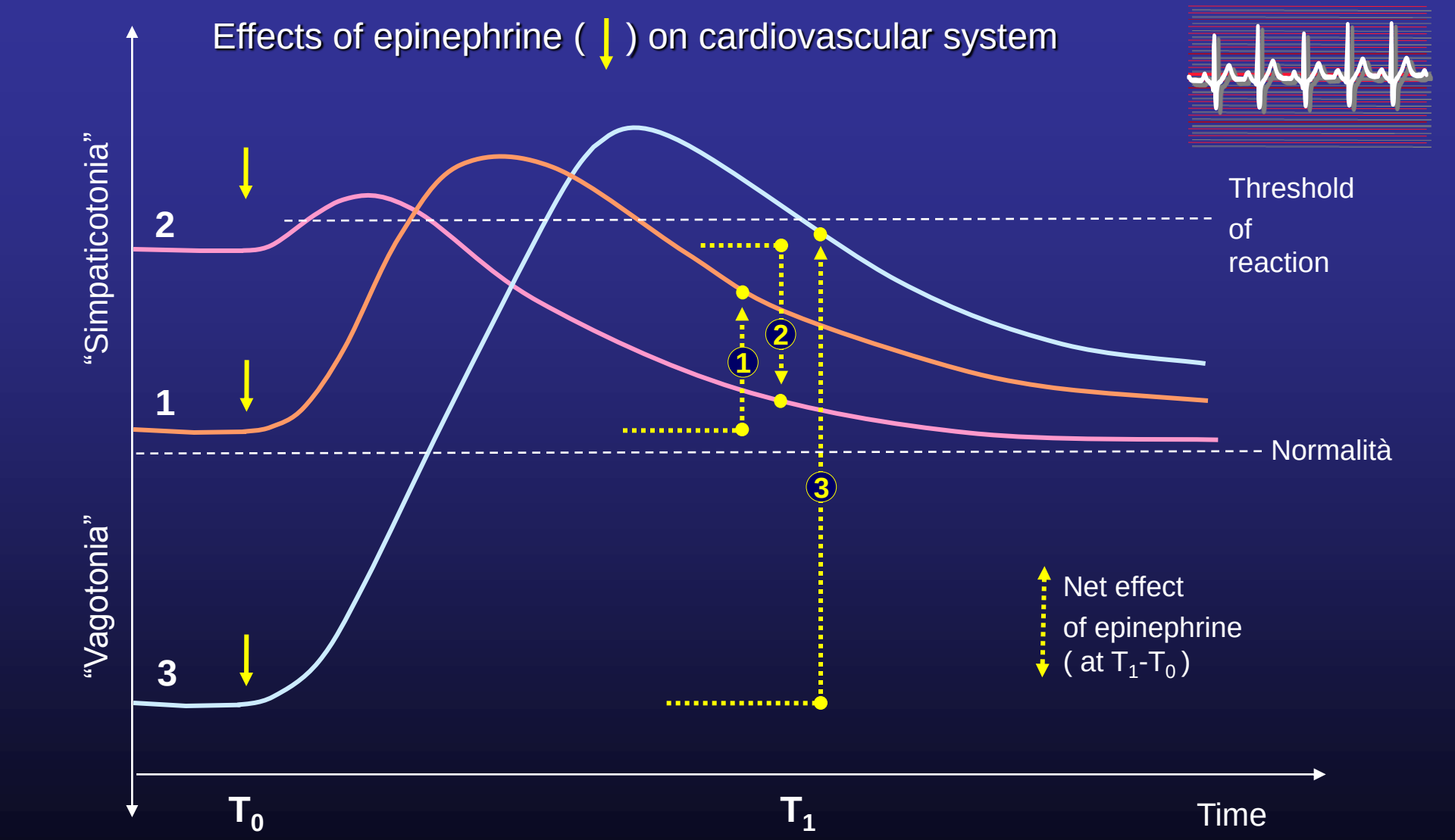
THE “RULE OF INITIAL VALUE” OF WILDER

J. Wilder: Das “Ausgangswert-Gesetz”, ein unbeachtes biologisches Gesetz und seine Bedeutung for Forschung und Praxis. *Zeit. d. Gesamte Neur. u. Psych*., vol. 137, p. 317, 1931.

- The final result of any vegetative reaction is dependent on the state of the organ, the degree of existing activity before treatment.
- The higher the level of activity prior to the stimulus, the lower the stimulating effect and the greater the inhibition phase of the reaction.
- If the status of the existing excitation reaches a high degree, for the presence of an agent system in an antagonistic way, the agents stimulants cause paradoxical reactions of inhibition.
- On the other hand, if we start from a very low activity, actions paradoxically stimulants are obtained with substances mormally acting as inhibitors.

THE «INITIAL VALUE RULE» of WILDER

See Bellavite et al. in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1876612/



IS PARADOXICAL PHARMACOLOGY WORTH PURSUING?

Richard A. Bond. TRENDS in Pharmacological Sciences Vol.22 No.6 June 2001, 273-276

- *Acute and chronic effects of drugs often produce opposite effects. This is particularly true for receptor-mediated events.*
- *For example, acute agonist exposure can produce activation of receptors and increased signalling, whereas chronic exposure can produce desensitization and decreased signalling.*

PARADOXICAL PHARMACOLOGY

Condition		β-agonists	β-antagonists
Congestive Heart Failure 	Acute	Beneficial ↑ contractility	Detrimental (feeling worse)
	Chronic	Detrimental ↑ mortality	Beneficial ↓ mortality

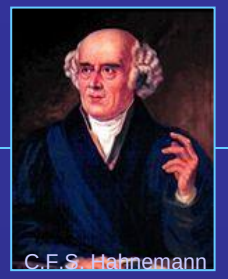
Data from the review of Bond, TIPS 22: 273-276, 2001

IS PARADOXICAL PHARMACOLOGY WORTH PURSUING?

Richard A. Bond. TRENDS in Pharmacological Sciences Vol.22 No.6 June 2001, 273-276

- *Can exacerbating a disease make use of the body's compensatory and redundant mechanisms to achieve a beneficial long-term response?*
- *Can we use drugs that, according to traditional views, would be considered to increase stress on the system in the short term, to actually treat and cure disease in the long term?*
- *Is it possible to exacerbate disease for a longer-term gain?*
- *Although there are several examples of where this strategy has appeared to work, a systematic testing of the hypothesis has not occurred and, for the majority of diseases, this hypothesis has never been tested*

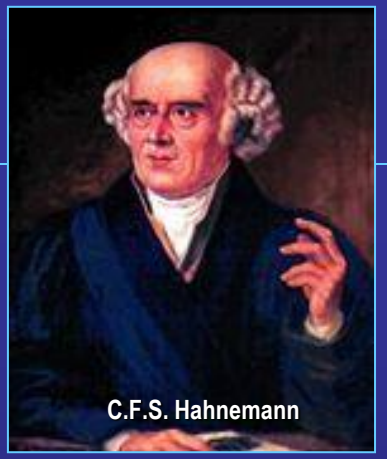
IS PARADOXICAL PHARMACOLOGY WORTH PURSUING?



"When medicines act as remedies, they can only bring their curative property into play by means of their power of altering man's state of health by the production of peculiar symptoms.
Therefore, we have to rely on the morbid phenomena which the medicines produce in the healthy body as the sole possible revelation of their in-dwelling curative power, in order to learn what disease-producing power, and at the same time what disease-curing power, each individual medicine possesses"

C.F.S. Hahnemann *Organon, par. 21*.

The scientific foundations of homeopathy



Wien 29 oct 2014
Prof. Paolo Bellavite - Università di Verona

2. The «simile» as inversion of effects

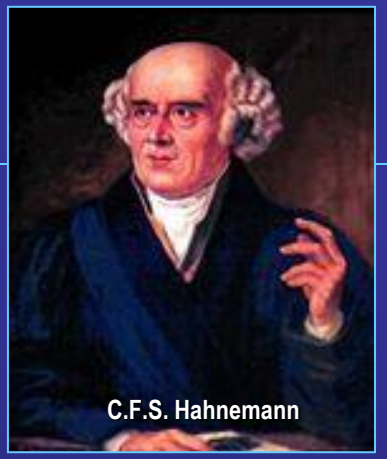
Synthesis:

There is widespread evidence that low doses can have inverse effects on a number of biologic systems

→ An active system can be inhibited by low doses of activators (e.g. bacterila peptides on leukocytes)

→ An inactive system can be stimulated by low doses of inhibitors (e.g. beta-blockers in heart failure)

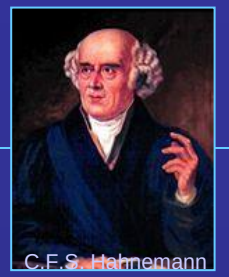
The scientific foundations of homeopathy



Wien 29 oct 2014
Prof. Paolo Bellavite - Università di Verona

1. Introduction: the wide field of homeopathic science
2. The «simile» as inversion of effects
   - The dose-response curves (Arndt-Schulz, Hormesis)
   - The state of the treated system (Wilder rule, paradoxical pharmacology)
3. How small the dose?

HOW SMALL SHOULD BE THE DOSE?



"How small, in other words, must be the dose of each individual medicine, homeopathically selected for a case of disease, to effect the best cure?"
"Is, as may easily be conceived, not the work of theoretical speculation. (...) Pure experiment, careful observation of the sensitiveness of each patient, and accurate experience can alone determine this in each individual case"

C.F.S. Hahnemann Organon, par. 278

THE MOLAR LAW

A. Avogadro (1776 – 1856)

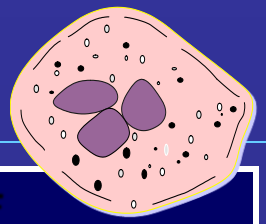
- Starting with a initial concentration of 10%, a dose of 10^{-24} M (~potency of 12 CH or 24D) corresponds to approx 1 molecule/liter.
- Dilutions higher than 12CH or 24D do not contain (in theory) any molecule of the original substance.

Since the initial concentration of active principles is usually much lower than 10%, it can be assumed that a dose of

10^{-20} Mol/L (~potency of 10 CH or 20D)

corresponds to the limit indicated by Avogadro's law)

EXAMPLES OF ULTRA LOW-DOSE EXPERIMENTS ("nanopharmacology" in the molecular range)

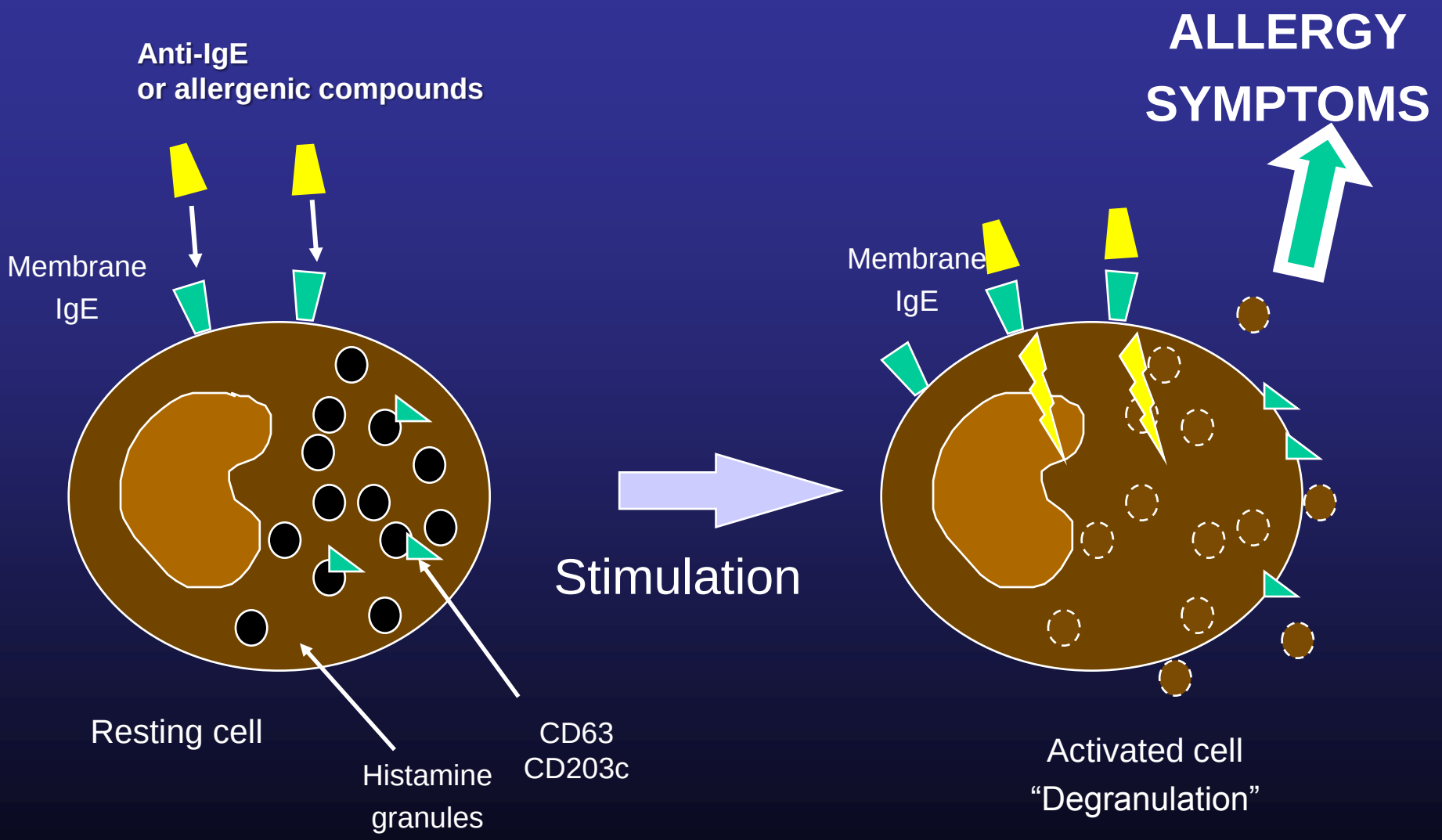


System	Agent	Concentr. (M)	Effect	Ref.
Neurons	Naltrexone	10^{-15}	**Paradoxical analgesia**	Crain 1995
NK cells	B-endorphin	10^{-17}	**Activation**	Williamson 1987
Monocytes	PAF	10^{-17}	**Activation**	Pleszczynski 1992
Macrophages	Opioid peptides	10^{-15}	**Inhibition**	Efanov 1994
Neutrophils	Substance P	10^{-16}	**Adhesion**	DeRose 1994
Neurons	ADNF peptide	10^{-16}	**Protects from cell death**	Brenneman 1996
T-lymphocytes	TGF-β	$4x10^{-18}$	**Migration**	Adams 1991
T-lymphocytes	Interleukin-1	$2x10^{-19}$	**Proliferation**	Orencole 1989
Hypophysis	Leukotrienes	10^{-18}	**Release of LH**	Gerozissis 1987
Mouse	Pregnenolone	10^{-21}	**Increases training memory**	Flood 1995
Rat	Gelsemine	10^{-14}-10^{-22}	**Activates allopregnanolone**	Venard 2008-2009

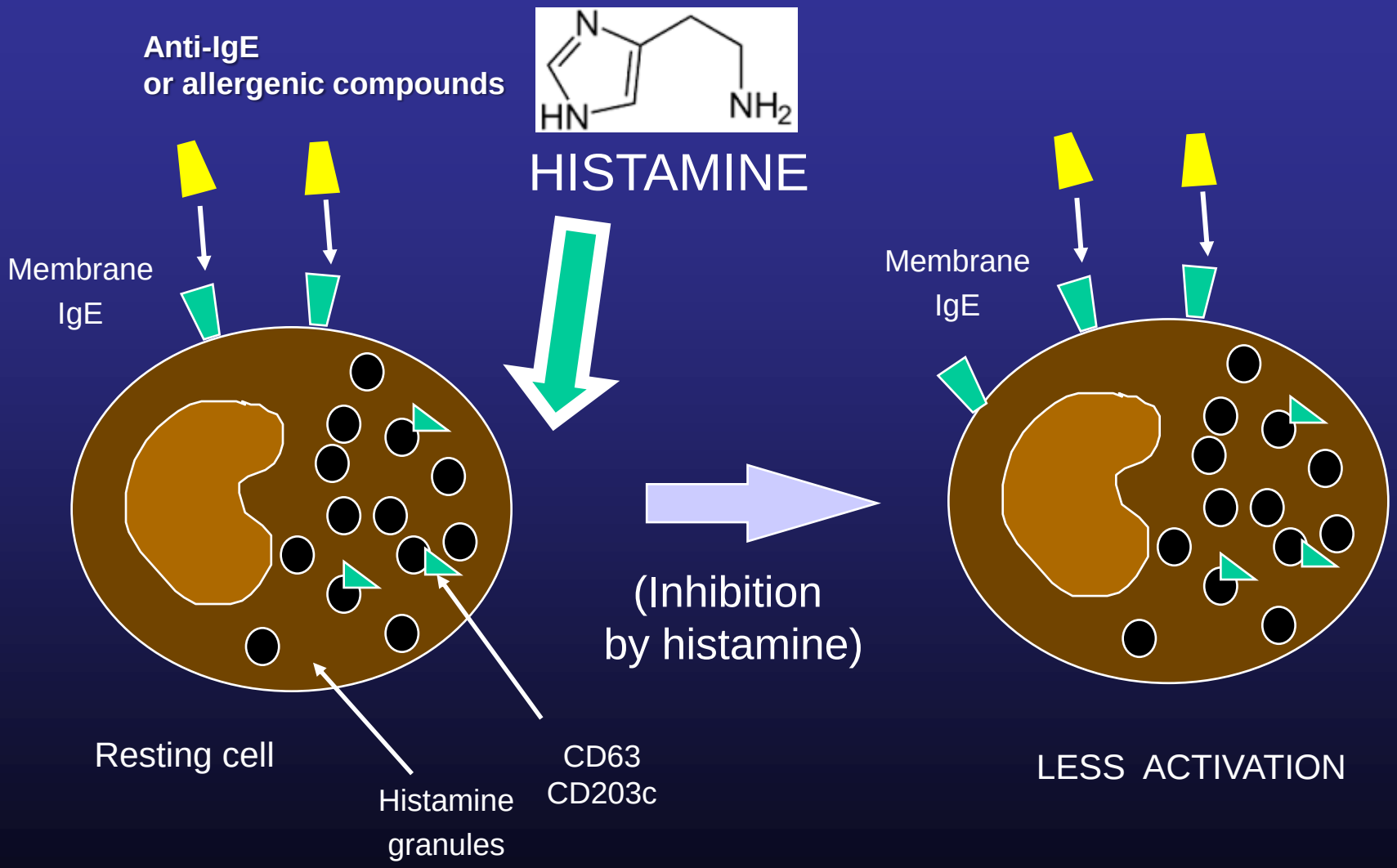
LABORATORY EVIDENCES OF "NANOPHARMACOLOGY" (High dilution-dynamization effects, Bbyond molecular range)

System	Agent	Dilution	Effect	Ref.
Human basophils	Histamine	10^{-24}	Inhibition	Belon 1999-2010- (and others including Chirumbolo -Bellavite)
Cicken embrio	Bursin	15 CH 10^{-27}g	Immunomodulatory and endocrine activity	Youbicier-Simo 1993-97
Rat Hypothalamus	Sodium chloride	10^{-60}	Reduces firing rate in rats under high-salt diet	Sukul 1991-98
Mice nervous system	Nux vomica	30 CH	Reduction of alchol-induced sleep time	Sukul 1999
Mouse blood	Acetylsalicylic acid	10^{-30}	Pro-thrombotic	Doutremepuich 1998
Mouse ears	Silica	10^{-60}	Speeds up wound healing	Oberbaum 1998
Wheat germination	Arsenic Silver nitrate	10^{-45} 26 D	Protect from toxicity Enhances growth	Betti 1997/2001 Pongratz 1998
Neurons	Cycloheximide	10^{-27}	Increases viability	Marotta 2002
Lymphocytes	Cadmium	15CH-20CH	Protects from cadmium toxicity	Wachli 2006
Mouse behaviour	Gelsemium	9CH-30CH	Anxiolytic-like effect	Bellavite 2009-12

THE MODEL OF BASOPHILS and Histamine



THE MODEL OF BASOPHIL and Histamine



THE MODEL OF BASOPHIL and Histamine HIGH DILUTIONS

Inflamm. Res.
DOI 10.1007/s00011-009-0044-4

Inflammation Research

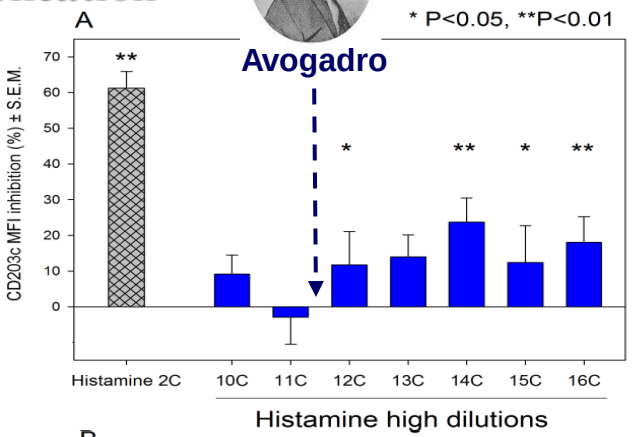
ORIGINAL RESEARCH PAPER

Inhibition of CD203c membrane up-regulation in human basophils by high dilutions of histamine: a controlled replication study

Salvatore Chirumbolo · Maurizio Brizzi · Riccardo Ortolani · Antonio Vella · Paolo Bellavite

Received: 14 November 2008 / Revised: 3 April 2009 / Accepted: 9 April 2009

Avogadro



Reports concerning the effect of highly diluted/succussed histamine on human basophils published in the mainstream literature

➢IN SUMMARY:

➢14 publications (2 with multicentre studies)

➢4 independent laboratories involved

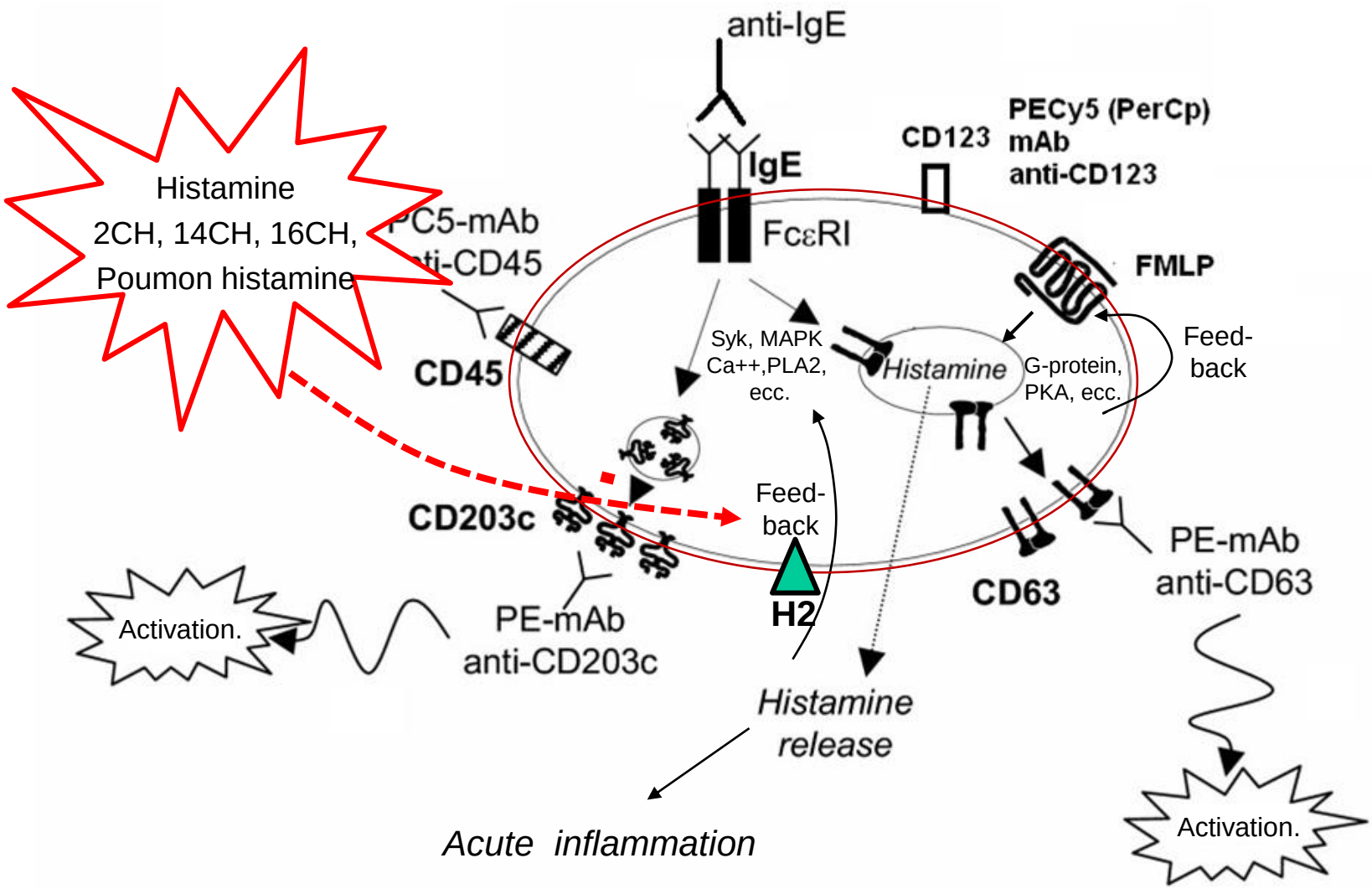
➢12 papers with positive results

➢ 1 negative

➢ 1 uncertain

- The amount of positive evidence is much higher than that usually accepted for conventional drgs.
- The lack of acceptation of this phenomenon is independent of the evidence, but is depending on on the pre-judgement, which is contrary to the scientific way of thinking.
- Anyway, high-dilution science needs a physical theory explaining those paradoxical results

Working model of the effect of histamine high dilutions: stimulation of H2 receptors triggering inhibitory feedback



NEW EXPERIMENTAL EVIDENCE OF HIGH-DILUTION EFFECTS

ARTICLE IN PRESS YHOMP521_proof ■ 2 October 2009 ■ 1/20

Homeopathy (2009) ■, 1–20

doi:10.1016/j.homp.2009.09.005, available online at http://www.sciencedirect.com

ORIGINAL PAPER

Assays of homeopathic remedies in rodent behavioural and psychopathological models

Paolo Bellavite[1,*], Paolo Magnani[1], Marta Marzotto[1] and Anita Conforti[2]

[1]*Department of Morphological Biomedical Sciences, University of Verona, Italy*
[2]*Department of Medicine and Public Health, University of Verona, Italy*

Effects in vivo model: *Gelsemium s.* on the anxiety-like behaviour of CD1 mice

Light-Dark

Magnani, Bellavite et al. Psychopharmacology 2010

Media ± SEM
of 6 experimenti
total
48 topi/gruppo

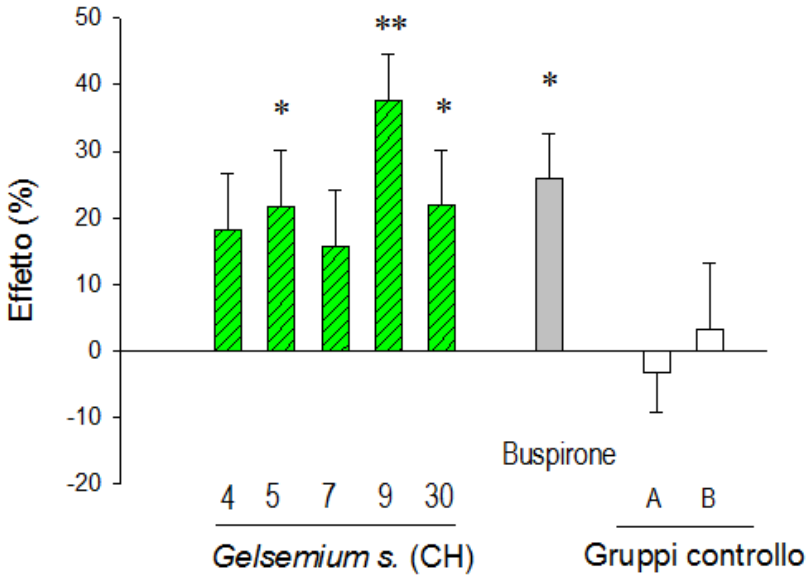
D: Global ANOVA for groups P=0.0004

E: Global ANOVA for groups P=0.0002

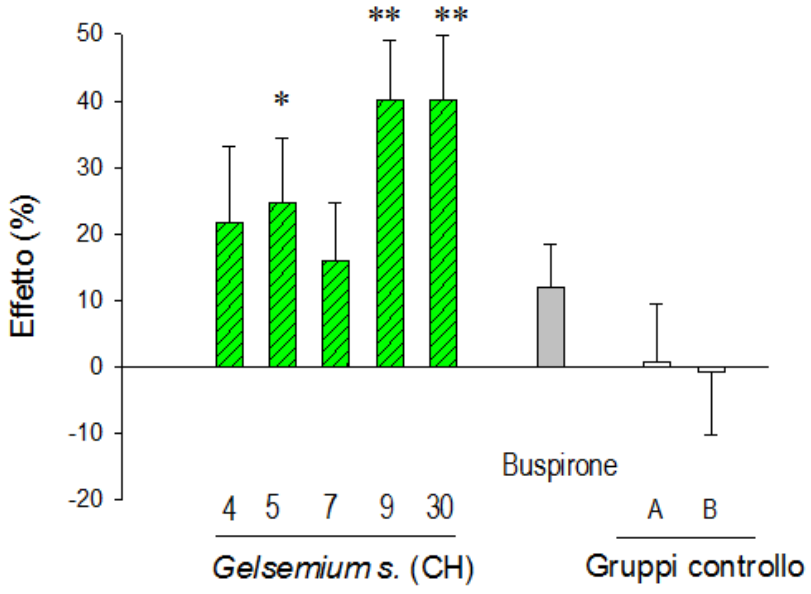
P* <0,05

P<0,001**

D: Light-dark: time spent in light (anxyolitic-like effect)



E: Light-dark: number of transitions



Gelsemium sempervirens

Fax reçu de : 0472164223
BOURON
20 rue de la Libération
F - 69110 SAINTE-FOY-LES-LYON

15-05-08 09:42 Pg: 1
CERTIFICAT D'ANALYSE
N° LIMS : 62477

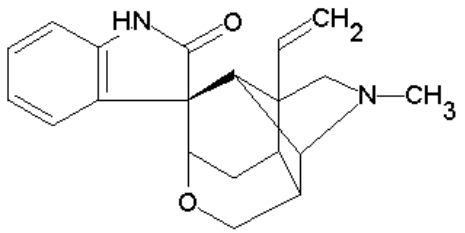
GELSEMIUM SEMPERVIRENS TM
G0B9.2TMGT1E

Date de fabrication	Quantité	N° de Lot
31 Mars 2005	173.1 L	TH0082

Date de contrôle	N° de contrôle
26 Avril 2004	C04046134

Partie Utilisée : Organes souterrains (1/10)
Description : Liquide jaune ambré, odeur aromatique.

ANALYSES	SPECIFICATIONS	RESULTATS
CARACTERES		
Couleur	conforme	conforme
IDENTIFICATION		
Chromatographie sur couche mince	conforme	conforme
ESSAI		
Teneur en éthanol	60 - 70 % V/V	63.7 % V/V
Méthanol	<0.05 %	<0.05 %
2-Propanol	<0.05 %	<0.05 %
Résidu sec	>0.50 %	1.37 %
DOSAGE		
Teneur en gelsémine	>0.010 %	0.021 %



Gelsemine
Molecular Weight: 322,41)

0,021% (MT)= 650 microMoles/L

1CH=6,5 microMoles/L

5CH=0,000000065 microMoles/L

9 CH= 0,00000000000000065 microMoles/L

Gelsemium 9CH: 1 molecule/mouse

10,000,000,000,000,000 times less molecules than standard dose of buspirone or diazepam

EFFECTS SHOWN BY MOLECULAR BIOLOGY TECHNIQUES

Marzotto *et al. BMC Complementary and Alternative Medicine* 2014, **14**:104
http://www.biomedcentral.com/1472-6882/14/104

BMC Complementary & Alternative Medicine

RESEARCH ARTICLE Open Access

Extreme sensitivity of gene expression in human SH-SY5Y neurocytes to ultra-low doses of *Gelsemium sempervirens*

Marta Marzotto[1], Debora Olioso[1], Maurizio Brizzi[2], Paola Tononi[3], Mirco Cristofoletti[1] and Paolo Bellavite[1*]

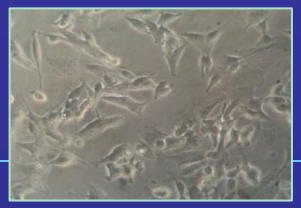
Abstract

Background: *Gelsemium sempervirens* L. (*Gelsemium s.*) is a traditional medicinal plant, employed as an anxiolytic at ultra-low doses and animal models recently confirmed this activity. However the mechanisms by which it might operate on the nervous system are largely unknown. This work investigates the gene expression of a human neurocyte cell line treated with increasing dilutions of *Gelsemium s.* extract.

Methods: Starting from the crude extract, six 100 × (centesimal, c) dilutions of *Gelsemium s.* (2c, 3c, 4c, 5c, 9c and 30c) were prepared according to the French homeopathic pharmacopoeia. Human SH-SY5Y neuroblastoma cells were exposed for 24 h to test dilutions, and their transcriptome compared by microarray to that of cells treated with control vehicle solutions.

Results: Exposure to the *Gelsemium s.* 2c dilution (the highest dose employed, corresponding to a gelsemine concentration of 6.5×10^{-9} M) significantly changed the expression of 56 genes, of which 49 were down-regulated and 7 were overexpressed. Several of the down-regulated genes belonged to G-protein coupled receptor signaling pathways, calcium homeostasis, inflammatory response and neuropeptide receptors. Fisher exact test, applied to the group of 49 genes down-regulated by *Gelsemium s.* 2c, showed that the direction of effects was significantly maintained across the treatment with high homeopathic dilutions, even though the size of the differences was distributed in a small range.

Conclusions: The study shows that *Gelsemium s.*, a medicinal plant used in traditional remedies and homeopathy, modulates a series of genes involved in neuronal function. A small, but statistically significant, response was detected even to very low doses/high dilutions (up to 30c), indicating that the human neurocyte genome is extremely sensitive to this regulation.



Microarray analysis of gene expression changes in human neurocytes

24h

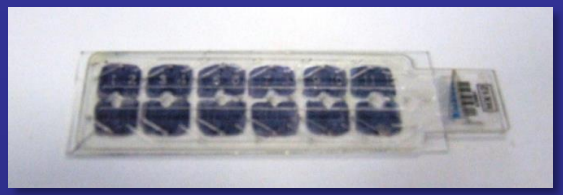
G30 G9 G5 G4 G3 G2

Ct3 Ct9 Ct5 Ct4 Ct3 Ct2

Gelsemium s. dilutions (G)

Control Dilutions (Ct)

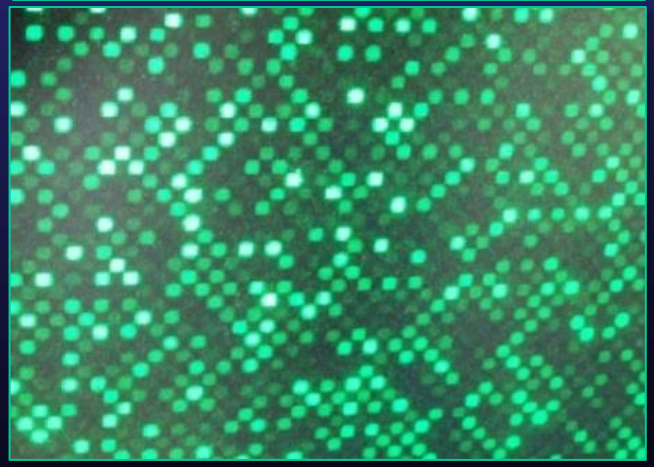
RNA →cDNA



12-samples microarray chip

4 independent replicate experiments

- **NimbleGen chip**
- Entire human transcriptome **(45034 genes!)**



Scanning and data analysis

BMC-Complementary Alternative Medicine March 2014

Exposure to the Gelsemium s. 2CH promoted the significant down-expression of 49 while 7 genes were overexpressed

Many of these 56 genes belong to:

- neuropeptide/receptor systems
- calcium signalling
- G-protein coupled transduction systems
- inflammatory pathways

DOWN

UP

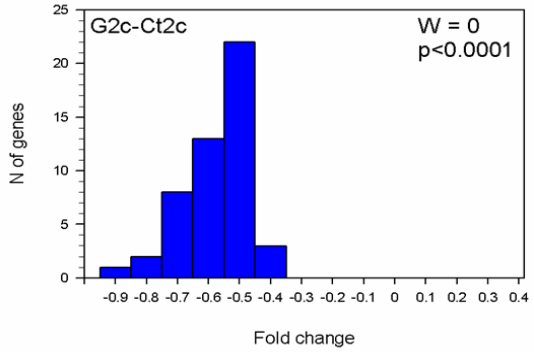
Gene ID	Transcript ID	Symbol	Log2 fold change			p^1	Description
7940	AF000424	LST1	-0.84	±	0.14	0.04	leukocyte specific transcript 1
390113	NM_001004726	OR4X1	-0.83	±	0.06	0.01	olfactory receptor, family 4, subfamily X, member 1
23746	AJ830742	AIPL1	-0.82	±	0.16	0.04	aryl hydrocarbon receptor interacting protein-like 1
284498	AL833920	C1orf167	-0.80	±	0.17	0.05	chromosome 1 open reading frame 167
221191	AK058068	Klkbl4	-0.79	±	0.12	0.04	plasma kallikrein-like protein 4
26658	NM_012377	OR7C2	-0.77	±	0.07	0.01	olfactory receptor, family 7, subfamily C, member 2
112401	BC039318	BIRC8	-0.76	±	0.11	0.00	baculoviral IAP repeat-containing 8
2848	NM_005298	GPR25	-0.75	±	0.15	0.02	G protein-coupled receptor 25
55803	NM_018404	ADAP2	-0.75	±	0.11	0.02	ArfGAP with dual PH domains 2
386676	NM_198690	KRTAP10-9	-0.73	±	0.12	0.04	keratin associated protein 10-9
4353	X04876	MPO	-0.72	±	0.15	0.04	Myeloperoxidase
N/A	AY358413	N/A	-0.71	±	0.18	0.02	Homo sapiens clone DNA59853 trypsin inhibitor
392391	NM_001001923	OR5C1	-0.71	±	0.05	0.04	olfactory receptor, family 5, subfamily C, member 1
N/A	AK094115	N/A	-0.70	±	0.11	0.04	Homo sapiens cDNA FLJ36796 fis, clone ADRGL2006817
55287	BC020658	TMEM40	-0.70	±	0.15	0.02	transmembrane protein 40
54209	NM_018965	TREM2	-0.69	±	0.10	0.02	triggering receptor expressed on myeloid cells 2
150365	AK097834	RP5-821D11.2	-0.68	±	0.17	0.02	similar to mouse meiosis defective 1 gene
400934	NM_207478	FLJ44385	-0.68	±	0.09	0.04	FLJ44385 protein
255061	NM_170685	TAC4	-0.67	±	0.14	0.01	tachykinin 4 (hemokinin)
644065	XM_931993	LOC644065	-0.65	±	0.23	0.04	hypothetical protein LOC644065
1339	NM_005205	COX6A2	-0.64	±	0.17	0.01	cytochrome c oxidase subunit VIa polypeptide 2
N/A	AK128093	N/A	-0.63	±	0.09	0.04	Homo sapiens cDNA FLJ46214 fis, clone TESTI4012623.
53841	AY358368	CDHR5	-0.63	±	0.11	0.04	mucin-like protocadherin
9332	NM_004244	CD163	-0.63	±	0.18	0.03	CD163 molecule
441239	XM_499305	LOC441239	-0.63	±	0.22	0.05	hypothetical gene supported by BC063653
7164	NM_001003397	TPD52L1	-0.62	±	0.09	0.02	tumor protein D52-like 1
11136	NM_014270	SLC7A9	-0.62	±	0.09	0.04	solute carrier family 7 member 9
389084	NM_206895	UNQ830	-0.62	±	0.11	0.04	ASCL830
400224	XM_375090	FLJ44817	-0.62	±	0.20	0.04	similar to pleckstrin homology domain protein (5V327)
647240	XM_934559	LOC647240	-0.60	±	0.06	0.00	hypothetical protein LOC647240
846	BC104999	CASR	-0.59	±	0.06	0.00	calcium-sensing receptor
116123	NM_138784	RP11-45J16.2	-0.58	±	0.09	0.04	flavin-containing monooxygenase pseudogene
644280	XM_497769	LOC644280	-0.58	±	0.06	0.05	hypothetical protein LOC644280
57452	AB032956	GALNTL1	-0.57	±	0.17	0.05	alpha-D-galactosamine N-acetylgalactosaminyltransferase
414301	NM_001001711	DDI1	-0.56	±	0.11	0.04	DDI1, DNA-damage inducible 1, homolog 1 (*S. cerevisiae*)
116535	BC016964	MRGPRF	-0.55	±	0.17	0.01	MAS-related GPR, member F
8811	NM_003857	GALR2	-0.55	±	0.07	0.04	galanin receptor 2
10880	NM_006686	ACTL7B	-0.55	±	0.12	0.04	actin-like 7B
6368	NM_145898	CCL23	-0.55	±	0.11	0.05	chemokine (C-C motif) ligand 23
64581	BC071746	CLEC7A	-0.54	±	0.08	0.04	C-type lectin domain family 7, member A
644003	XM_927256	LOC644003	-0.54	±	0.11	0.04	similar to Mucin-2 precursor (Intestinal mucin 2)
643514	XM_931594	LOC643514	-0.54	±	0.10	0.03	hypothetical protein LOC643514
374569	XM_935431	LOC374569	-0.54	±	0.07	0.04	Similar to Lysophospholipase
84504	BC101635	NKX6-2	-0.53	±	0.13	0.03	NK6 transcription factor related, locus 2 (Drosophila)
732	NM_000066	C8B	-0.53	±	0.06	0.05	complement component 8, beta polypeptide
146336	NM_182510	FLJ32252	-0.52	±	0.03	0.01	hypothetical protein FLJ32252
150763	BC042847	LOC150763	-0.51	±	0.10	0.04	hypothetical protein LOC150763
2020	NM_001427	EN2	-0.51	±	0.08	0.04	engrailed homolog 2
646258	XM_929203	LOC646258	-0.51	±	0.11	0.04	hypothetical protein LOC646258
154872	NM_001024603	LOC154872	0.51	±	0.10	0.03	hypothetical LOC154872
400866	NM_001001789	C21orf24	0.52	±	0.12	0.05	chromosome 21 open reading frame 24
9457	NM_020482	FHL5	0.55	±	0.19	0.04	four and a half LIM domains 5
55816	NM_018431	DOK5	0.56	±	0.04	0.03	docking protein 5
1446	NM_001890	CSN1S1	0.57	±	0.09	0.04	casein alpha s1
285600	AK130941	KIAA0825	0.63	±	0.06	0.01	KIAA0825 protein
57538	NM_020778	ALPK3	0.76	±	0.10	0.01	alpha-kinase 3

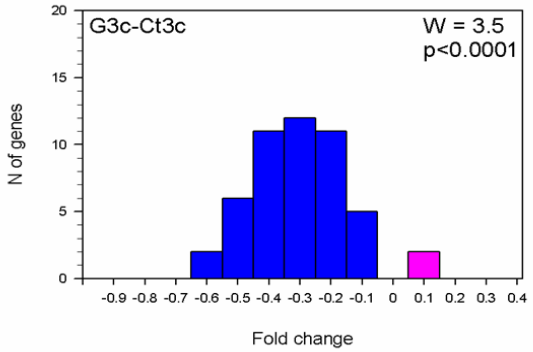
Effects of Gelsemium on expression of 49 Gels C2-down-regulated genes

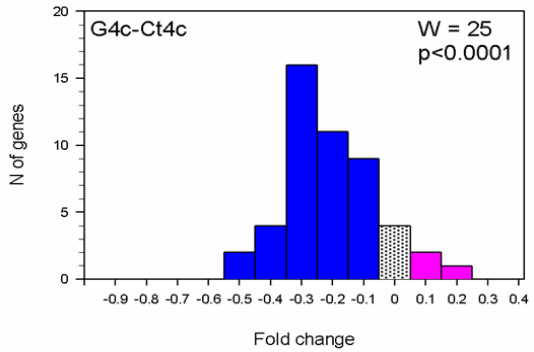
[Gelsemine]= 1.3 x10^{7} molecule/cell

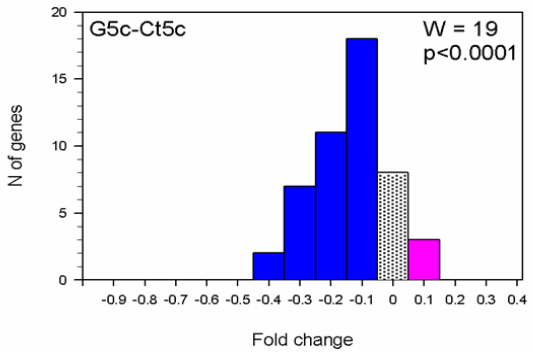
1.3 x 10^{3} molecule/cell

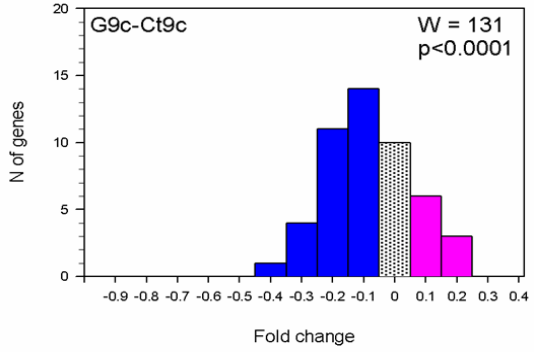
0 molecule/cell

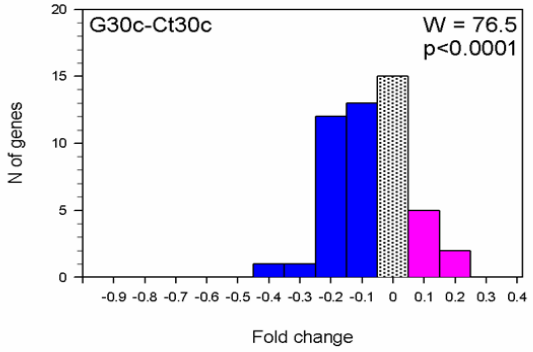












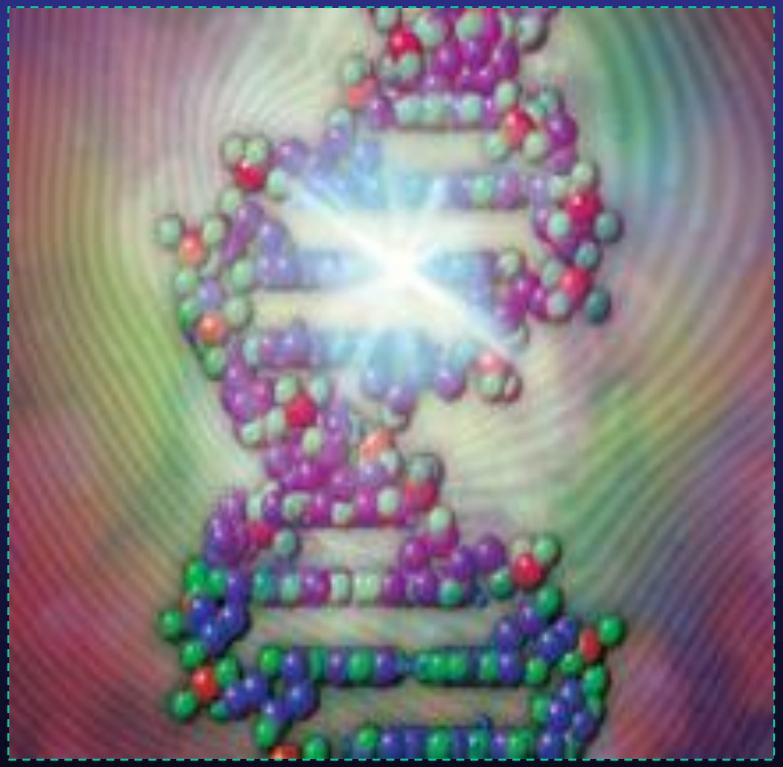
1.3 x10^{5} molecule/cell

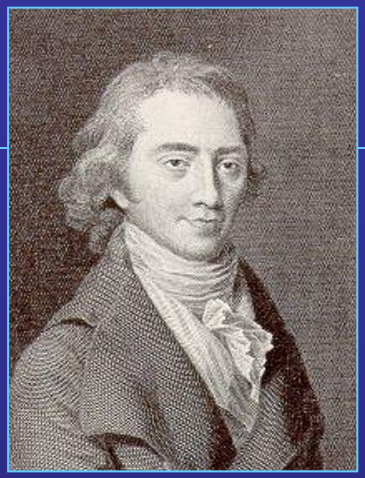
13 molecules/cell

0 molecule/cell

In human neurons 49 Genes among 45034 tested are regulated by high dilutions of Gelsemium sempervirens

NEW SPACE FOR SCIENTIFIC HOMEOPATHY!



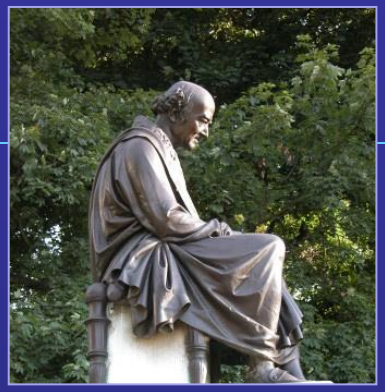


INTEGRATIVE MEDICINE AND HOMEOPATHY

C.W.Hufeland (1762-1836)

"No homeopathy, but indeed a homeopathic method in rational medicine.
No homeopaths but indeed rather physicians who employ the homeopathic method at he right time and place.
The special and most beautiful task of homoeopathy remains: to find and seek for new specific agents"

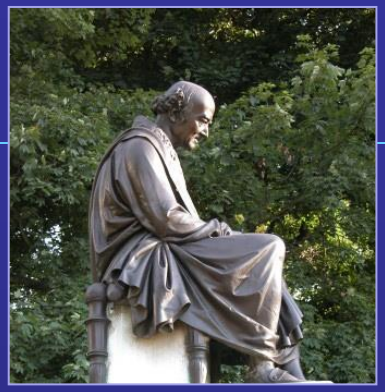
Quoted from C.W.Hufeland, In: L.J. Boyd. *A Study of the Simile in Medicine* , Boericke and Tafel, Philadelphia,1936. p. 147



THE «SIMILE» IN THREE POINTS

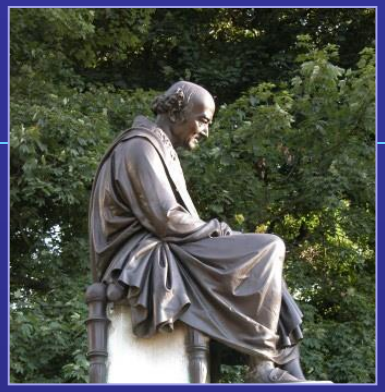
1. The “similia” (or similarity) principle holds that the medicine capable of regulating a diseased organism (individualized homeopathic therapy) is the same medicine which is capable of inducing a similar pattern of symptoms in a healthy organism.

   Homeopathic pharmacopoeia is grown with careful experimentation of hundreds of substances on healthy people to detect their specific and global perturbing power.



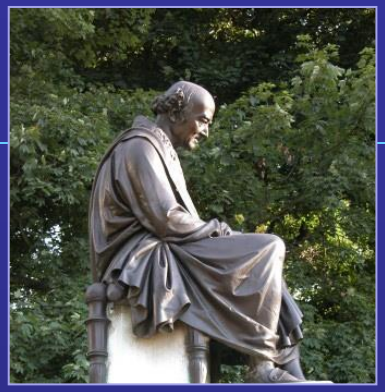
THE «SIMILE» IN THREE POINTS

2. The therapeutic similarity of drug action may be fundamentally based on the widespread phenomenon of inversion of biological effects dependent on the dose of the substance (Arndt-Schulz rule, hormesis, in homeopathic terms, dilution and “dynamization”) and/or on the physiological state of the receiver organism (stressed living systems may have opposite reactions to the same drug as compared with normal systems).



THE «SIMILE» IN THREE POINTS

3. The medicine that has been chosen according to the similia principle may be perceived by specific and sensitive (“primed”) regulatory systems - that have a crucial role in the dynamic of the diseaseas - as a stress signal, which may trigger an inverse effect that shifts the targeted system (cell, tissue, or whole organism) toward a correct new dynamical equilibrium, proximal to the healthy state.



THE «DOSE» IS A REAL PROBLEM?

The pharmacological information of homeopathic medicines may have either chemical nature (ultra-low-dose, with still presence of molecules of active principle) or chemio-physical nature (high-dilution/dynamization, where information is carried by the solvent nanoparticles), or both.