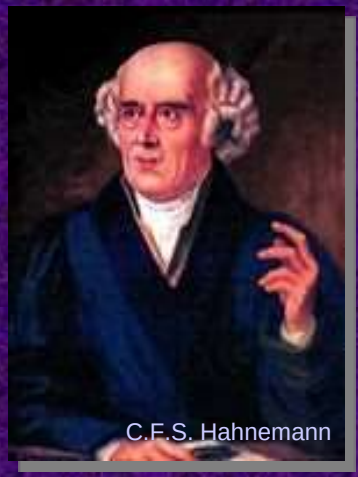
CUTTING EDGE RESEARCH IN HOMEOPATHY
ROME 2015



Basic research on homeopathic principles

Paolo Bellavite, Marta Marzotto, Debora Olioso, Clara Bonafini

University of Verona

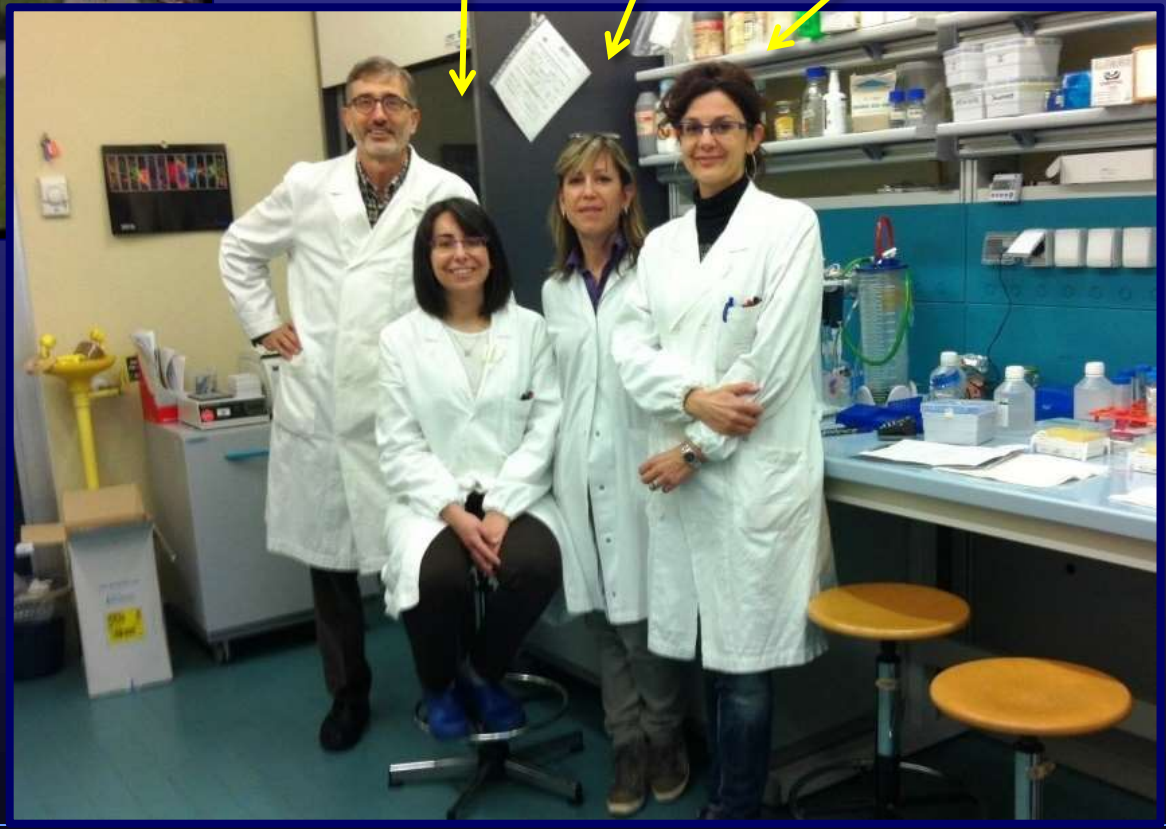
Buon giorno! Good morning! 早安！

Verona Integrative Medicine Research Group (y. 2015)

Clara Bonafini

Marta Marzotto

Debora Olioso



We thank for research grants:
- Boiron Laboratoires
- Italian Research Ministry

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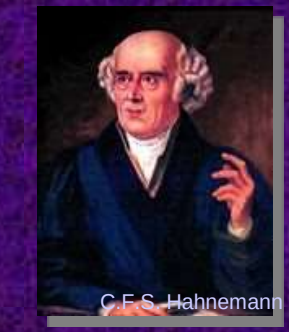


Basic research on homeopathic principles
Summary

1. Introduction (motivation)
2. Studies in animal and plant models
3. In vitro laboratory studies
4. Perspectives

THE MOTIVATION AND IMPULSE TO BASIC RESEARCH IN HOMEOPATHY

Jos Kleijnen

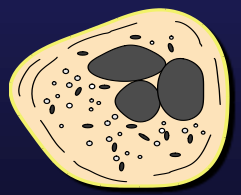
any unpublished trials and to get further details of the published ones. We used strict criteria to select the best trials and based our main conclusions on the results of these. The amount of positive evidence even among the best studies came as a surprise to us. Based on this evidence we would be ready to accept that homoeopathy can be efficacious, if only the mechanism of action were more plausible. The way in which the belief of people changes after the presentation of empirical evidence depends on their prior beliefs and on the quality of the evidence.

Kleijnen, J., Knipschild, P. & Ter Riet, G. **1991**. Clinical trials of homoeopathy. *Brit. Med. J.* **302**: 316-323.

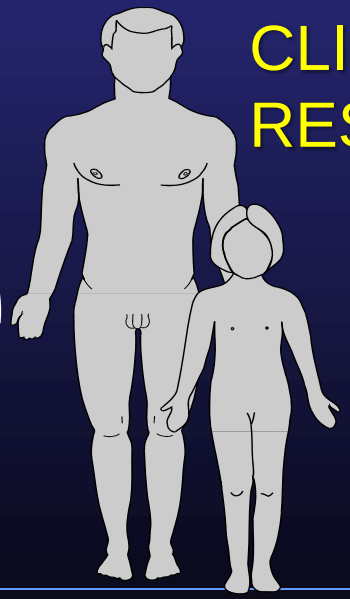
The two major PRINCIPLES to be investigated

- The same substance or similar substances can have opposite (inverse) effects in different conditions:
  a) **doses** or
  b) **sensitivity** of the target system
- Pharmacological power of the original substance is retained (or even enhanced?) in serial **dilutions with succussion**

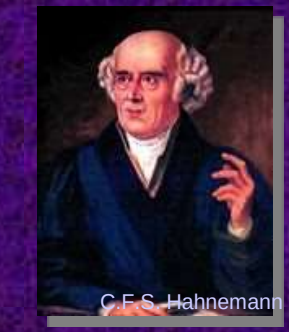
BASIC RESEARCH



CLINICAL RESEARCH



CUTTING EDGE RESEARCH IN HOMEOPATHY
ROME 2015



Basic research on homeopathic principles

1. Introduction (motivation)
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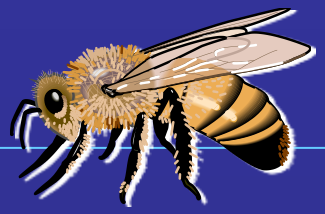
EXAMPLES OF STUDIES IN WHOLE ORGANISMS (ANIMALS AND PLANTS)

System	Agent	"Conventional" effect	"Homeopathic" effect	Ref.
Rat, Guinea pig	Histamine Lung Histamine Apis mell.	Pro-inflammatory agent	Histamine (30x), Lung histamine (18c) and Apis mellifica (7c/10c) reduce inflammation symptoms	Bastide 1975,Poitevin 1988, Bildet 1990 Conforti 1993
Rat, Mouse	Arsenic	Whole body and liver toxicity	Ars. high dilutions (7c-30c) protect from intoxication	Lapp 1955; Wurmser 1955; Cazin1987-1991; Banerjee,P, Khuda-Bukhsh 1998-2000
Rat	Nux vomica	Neurohinibition (strychnine)	Reduces alchool-indced sleeping time	Sukul et al., 1999
Rat	Aspirin	Antithrombotic	Aspirin 10^{-30} g/kg (15c) has pro-thrombotic effects	Beulogne-Malfatti,Doutreme-puich , Eizayag et al. 1998-2012
Rat	Phosphorus	Hepatotoxicity	Phosphorus high dilutions (30x) protects from toxic hepatitis	Bildet 1984, Guillemain 1987 Palmerini 1993
Tadpoles	Thyroxine	Increases the rate of metamorposis	Thyroxine high dilutions (up to 30x) inhibit metamorphosis	Endler 1990-2014, Lingg 2008, Weber 2008, Guedes 2011, Harrer 2013
Rat, Mouse	Gelsemium s.	Toxic and convulsivant	Anxiolytic effect (2c-30c) of Gelsemium s.	Magnani 2010, Venard 2011, Bellavite 2012
Wheat	Arsenic	Cell toxicity	Ars. high dilutions (45x) stimulate vitality	Betti et al. 1997-2014

Developments of experimental studies on APIS M. (1975-2015)



Madleine Bastide (1935-2007)

1975 ➢Homeopahtic dilutions (7C-9C) of bee venom (*Apis mellifica* and *Apium virus*, have a **protective and curative effect on X-ray induced erythema in albino guinea pig** (Bastide1975, Bildet1989, 1990)

1988 ➢High dilutions of *Apis mellifica* **inhibit basophil degranulation** (histamine release) (Poitevin et al., 1988)

1993 ➢Our group studied the effects of homeopathic preparations of *Apis mellifica* (and *Histamin)* on rat paw edema induced by the injection of inflammatory doses of histamine. High dilutions of up to 30D had a **small but significant inhibitory effect on the development of edema** (Conforti et al.,1993).

2004 ➢We described a **small inhibiting effect of *Apis mellifica*** (4 D, oral drops) in the carrageenan-induced edema in rats .

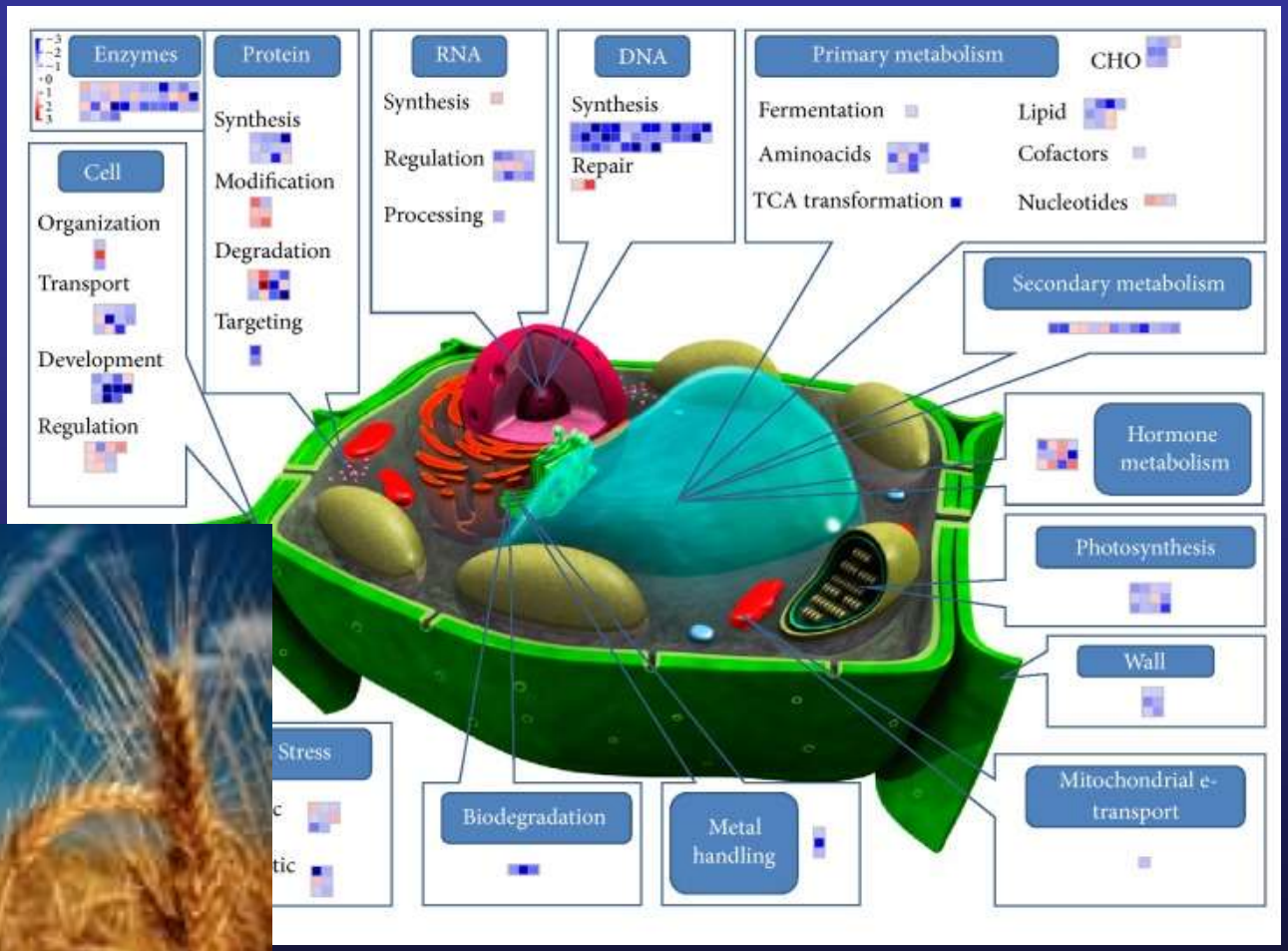
2014 ➢Bigagli and coworkers (2014) showed with microarray techniques that *Apis mellifica* TM modifies **expression of hundreds of genes** in human prostate epithelial cells; dynamized dilutions (3C, 5C and 7C) still exert significant effects on genes involved in inflammation and oxidative stress

Thyroxine/tadpoles studies (1990-2015!)

Christian Endler

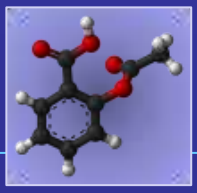
Arsenic/plant studies (1994-2015!)

Lucietta Betti



«AGRO-HOMEOPATHY»?

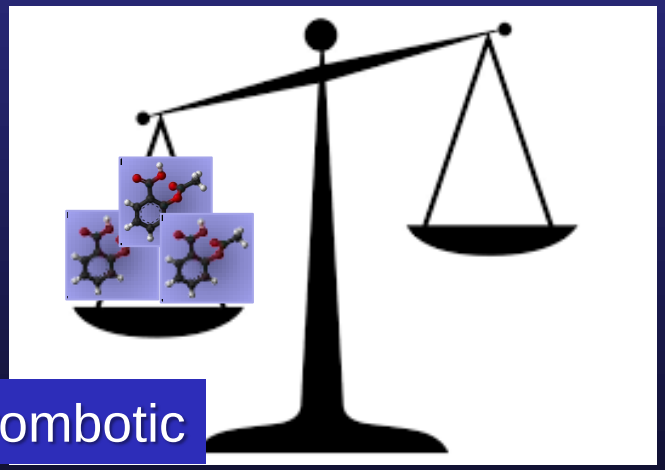
INVERSE EFFECTS OF ASPIRIN (1990-2013…!)



Dr Christian Doutremepuich

Dr Francisco Eizayaga

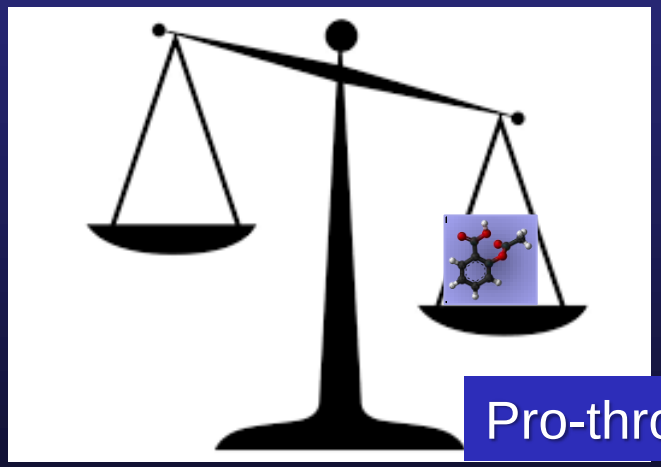
High dose (500 mg)
Low dose (50-100 mg)



Anti-thrombotic

(Pro-haemorragic) → Adverse effect

Ultra-low dose (5CH)
High dilution (15-30CH)



Pro-thrombotic

Homeopathic use? ← (Anti-haemorragic)

Our studies in mice behavioral models (2007-2012)



1. **First series (→ECAM J 2009):**
   - →8 replication experiments with *Gelsemium s.* 5C
   - →3 replication experiments with *Gelsemium s.* 7C
   - →2 replication experiments with *Gelsemium s.* 30C
   - Positive control: 8 replications with Diazepam

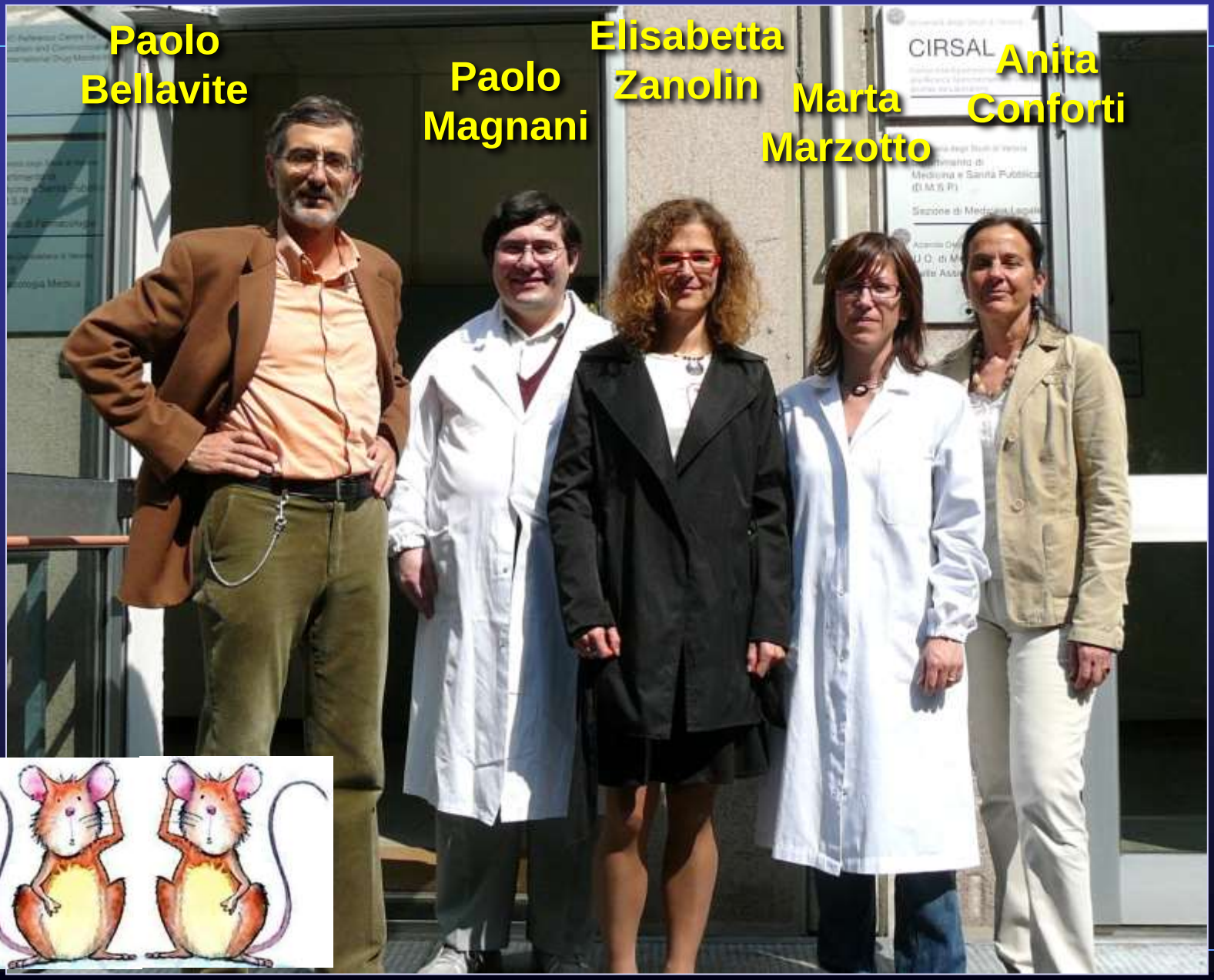
2. **Second series (→Psychopharmacology 2010):**
   - → 6 replication experiments with *Gelsemium s.* 4C, 5C, 7C, 9C, 30C
   - Positive control: 5 replications with Buspirone
     1 replication with Diazepam

3. **Pooled data analysis of the two series With Gelsemium s. (→ECAM J. 2012)**

4. **Other Drugs:**
   - → 4 replication experiments with Aconitum 5C, 7C, 9C, 30C
   - → 5 replications with Ignatia 4C, 5C, 7C, 9C, 30C

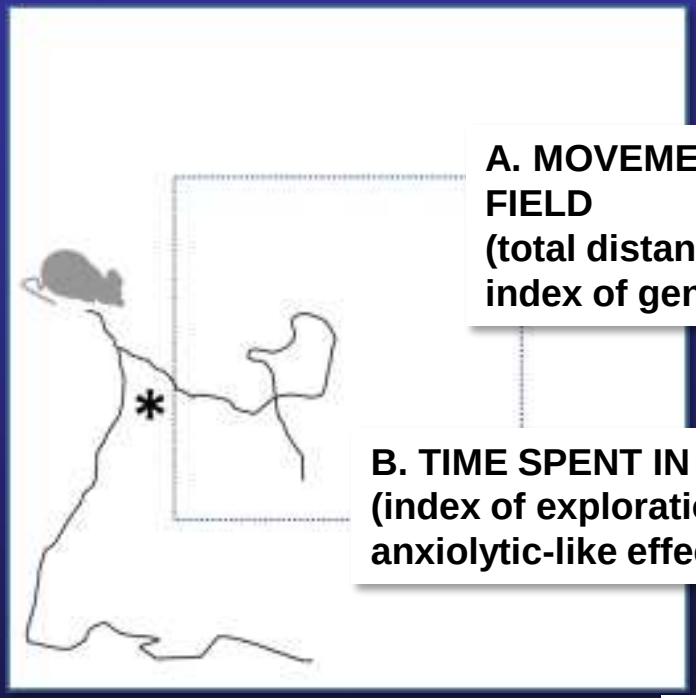
Note: each replication experiment lasts about 4 weeks

Homeopathic research team in mice models (2007-2012)



Behavioural models used

Open Field

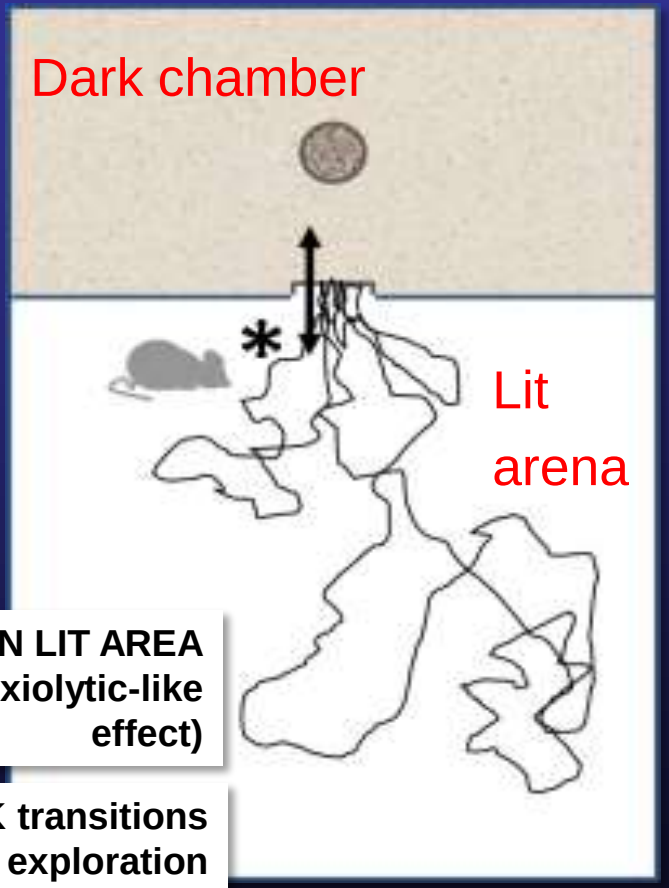


A. MOVEMENT IN WHOLE FIELD
(total distance travelled, index of general function)

B. TIME SPENT IN CENTRAL AREA
(index of exploration attitude, anxiolytic-like effect)

- *Double blind*
- *Ethological models*
- *No stress or pain to animals*

Light-Dark choice

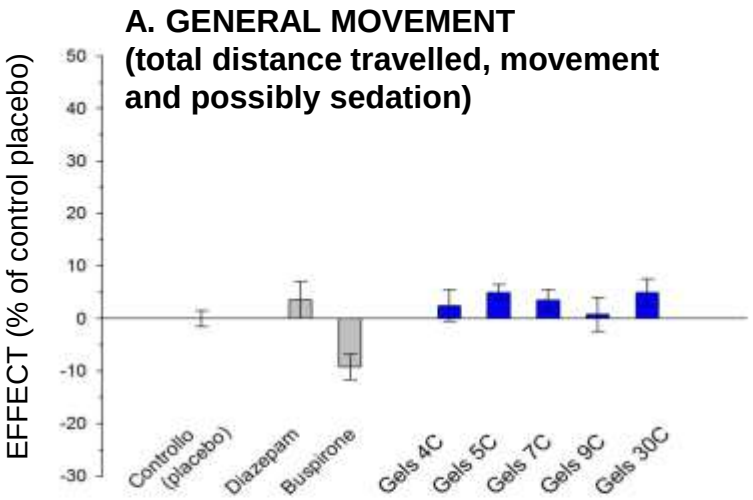


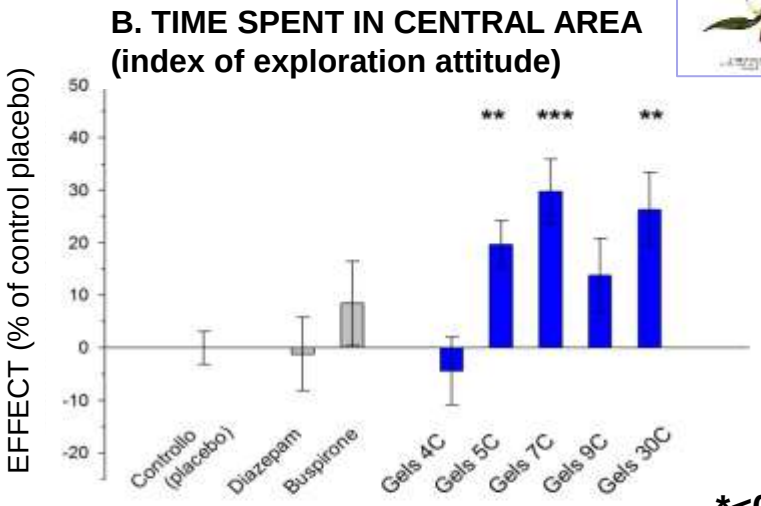
C. TIME SPENT IN LIT AREA
(no aversion to light, anxiolytic-like effect)

D. LIGHT-DARK transitions
(anxiolytic-like effect exploration attitude and movement)

POOLED DATA ANALYSIS (14 complete experiments)
Evidence-Based Complementary and Altern. Med., 2012

Open field





***<0.05**

****<0.01**

*****<0.001**

POOLED DATA ANALYSIS (14 complete experiments)
Evidence-Based Complementary and Altern. Med., 2012

Notes:

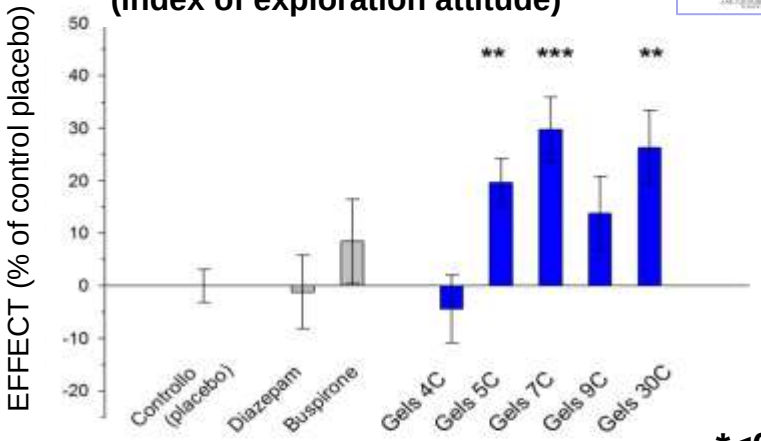
7c,9c,30c > 4c, 5c

No «inversion of effects» (good thing)

No hormesis

Striking non-linearity

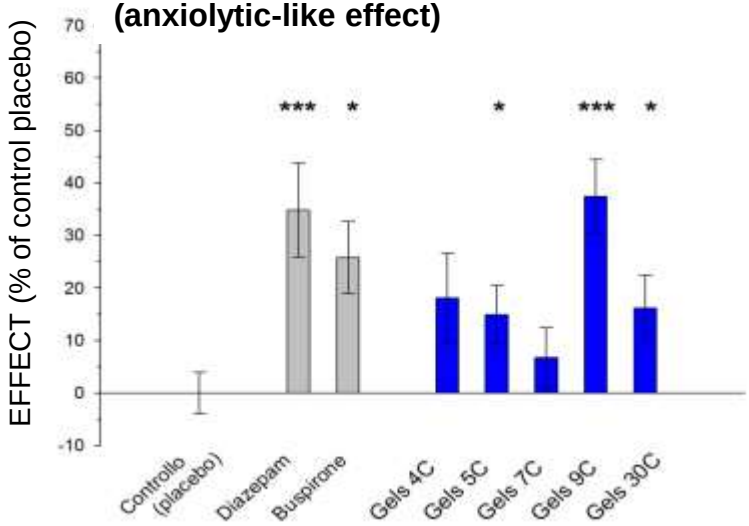
B. TIME SPENT IN CENTRAL AREA
(index of exploration attitude)



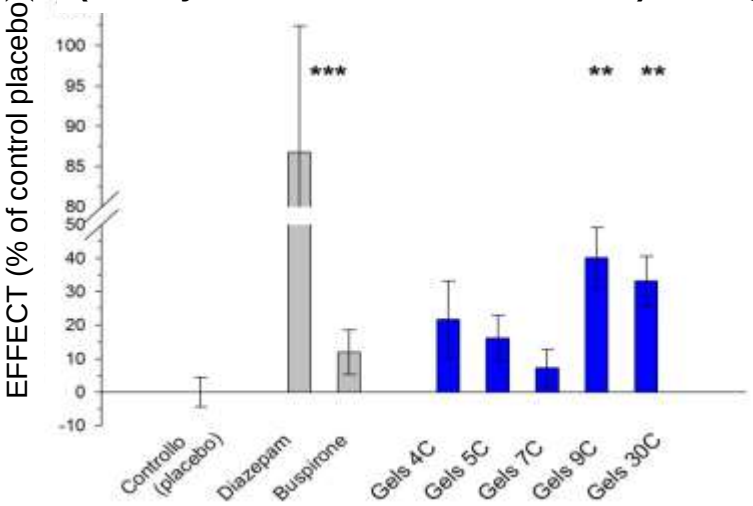
*<0.05
**<0.01
***<0.001

Light
Dark

C. TIME SPENT IN LIT AREA
(anxiolytic-like effect)

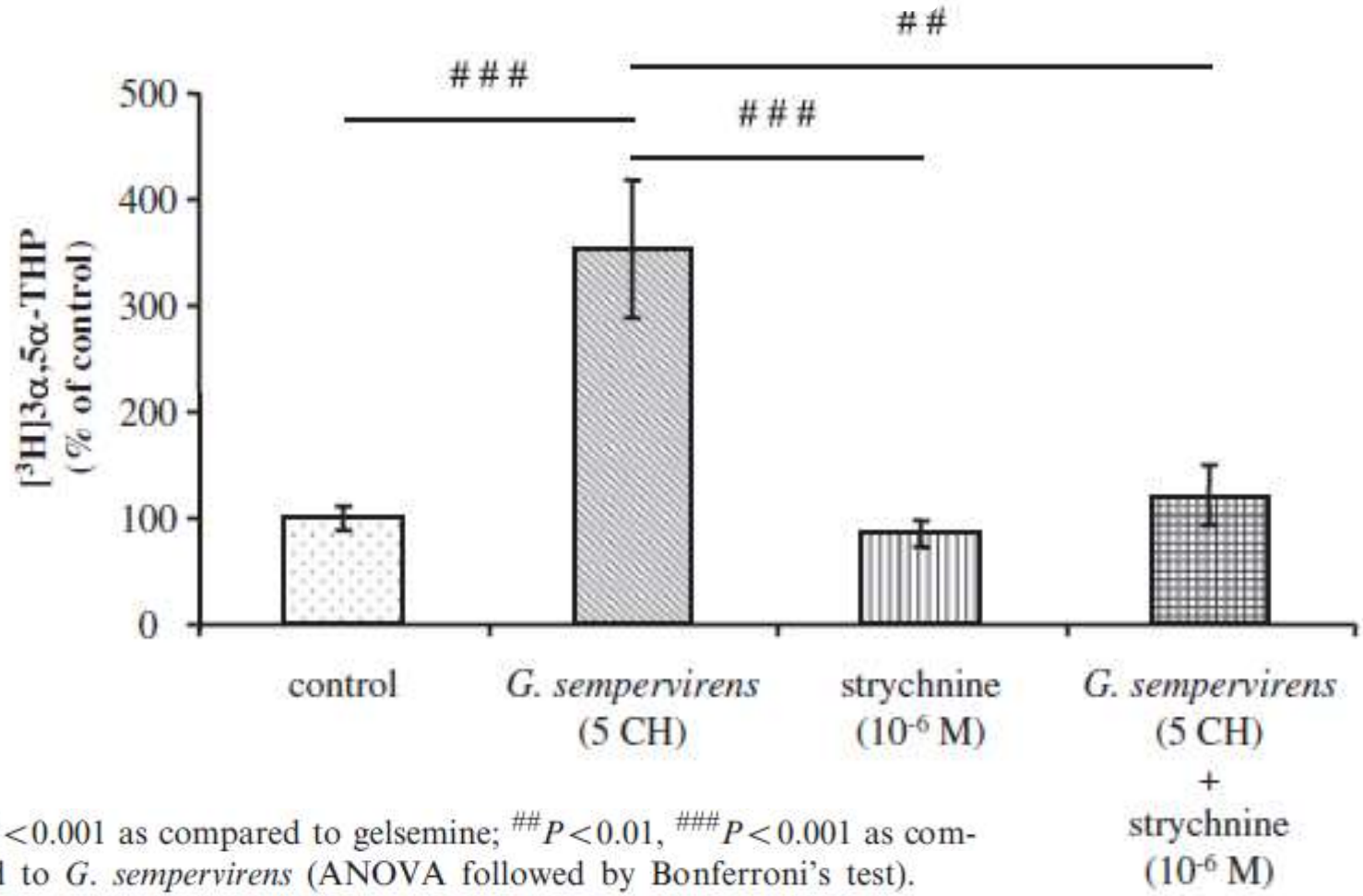


D. LIGHT-DARK transitions
(anxiolytic-like effect and movement)



Gelsemium sempervirens Activity on Neurosteroid Allopregnanolone Formation in the Spinal Cord and Limbic System of Rats

Adapted from: Christine Venard et al., ECAM-2011



***$P < 0.001$ as compared to gelsemine; ##$P < 0.01$, ###$P < 0.001$ as compared to *G. sempervirens* (ANOVA followed by Bonferroni's test).

Gelsemium s. in mice: KEY-NOTES

- **Reproducible and significant effects in behavioral models in mice, concerning a subset of "symptoms" :**
  - aversion to open space
  - amelioration with movement
  - feeling in a danger
  - aversion to light

- **No adverse effects on general locomotion (an effect shown by buspirone in chronic treatment)**

- **NON-LINEARITY (various activity peaks) with increasing potencies, BUT in general different potencies have the same trend of effects (important for practical purposes). 7c-9c-30c higher effects than 4c and 5c**

- **Hypotheses of action mechanism: stimulation of glycine receptors and thus neurosteroid synthesis with consequent increase of GABA inhibitory effects (Venard et al 2011). More recently we also showed an effect on prokinecitine receptors (Olioso et al. 2014)**

UP-TO DATE CONCLUSIONS FROM ANIMAL AND PLANT MODELS

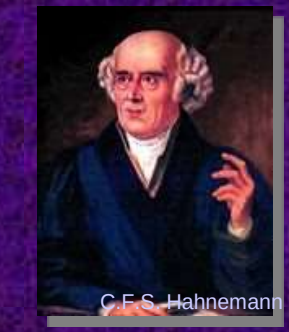
- Confirmation of the "**similia principle**": homeopathic dilutions counteract toxicity of ponderal doses (e.g. *Arsenic*, *Phosphorus*)
- Confirmation in animals of some **symptoms** reported by Materia Medica (e.g. *Gelsemium, Apis, Histaminum*)
- Hope of possible applications in **agro-homeopathy**
- Consistent evidence that high dilutions (even beyond Avogadro) have reproducible effects different from control solutions: **end of "placebo story"**

End of “placebo story”?

~~HOMEOPATHY IS ONLY A PLACEBO!~~

HOMEOPATHY CAUSES ADVERSE EFFECTS!

CUTTING EDGE RESEARCH IN HOMEOPATHY
ROME 2015



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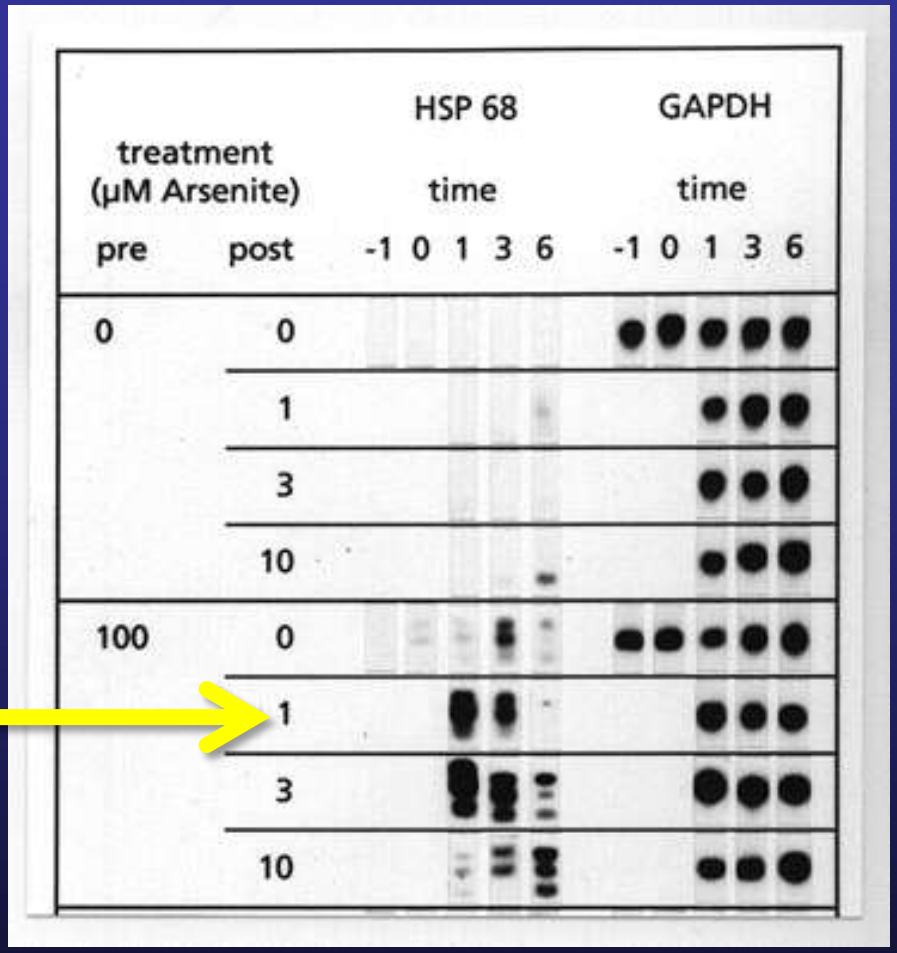
EXAMPLES OF INVERSE EFFECTS IN LABORATORY SYSTEMS

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 and 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, Puzzo 2008
Epithelial and Tumor cells	Oxidants	Short-term/high doses decrease viability	Long-term/low doses increase viability	Da Silva 1996 Jenkins 1995
Macrophages	Interferons 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
Neutrophils	Podophyllum	Metabolic inhibition	Metabolic priming and stimulation	Chirumbolo and Bellavite 1997

Post-conditioning Hormesis: beneficial effects of low doses of a toxic substance

Roeland van Wijk

STIMULATION OF SELF-RECOVERY BY LOW DOSES OF ARSENITE IN ARSENITE-INTOXICATED CELLS. (F.A.C. WIEGANT, R. VAN WIJK et al.)



The influence of a step-down arsenite treatment on the induction of hsp68-mRNA.

POSSIBLE MODELS EXPLAINING INVERSE EFFECTS (= SIMILIA PRINCIPLE) AT A CELLULAR LEVEL

References in www.paolobellavite.it
And recent papers in Journal «Homeopathy»

- Detoxification enzymes (gene expression and enzyme activation)
- Heat shock proteins (stress proteins, chaperonins)
- Various receptors (different affinity and different coupling with signal transduction pathways)
- Gating theory (signal transduction)
- "Hormesis" (includes all the previous mechanisms): YES for low dilutions (ponderal doses); doubts for high dilutions.

Amedeo Avogadro (1776 – 1856)

FROM LOW DOSES TO HIGH DILUTIONS: THE MOLAR LAW

- Dilutions of 1 Mol/L substance beyond 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 1 Mol/L, it can be assumed that a potency of 10 CH or 20D) corresponds to the limit indicated by Avogadro's constant: **6.02×10^{23}**)

Example: *Gelsemium* TM = 6.5×10^{-4} Mol/l of gelsemine

Gelsemium 5c = 6.5×10^{-14} Mol/l of gelsemine

Gelsemium **10c = 6.5×10^{-24}** Mol/l of gelsemine

EXAMPLES OF HIGH DILUTION EFFECTS "*IN VITRO*"

System	Agent	Dilution	Effect	Ref.
Human basophils	Apis, Histamine	12CH-16CH $10^{-24} \rightarrow 10^{-32}$	Inhibition of activation markers	Poitevin 1988, Belon 1999-2009 (and Verona Group)
Human basophils	Adrenaline	12CH-16CH $10^{-24} \rightarrow 10^{-32}$	Inhibition of activation markers	Mannaioni et al. 2010
Cicken embrio	Bursin	15 CH (10^{-27}g)	Immunomodulatory and endocrine activity	Bastide, Youbicier-Simo 1993-97
Human neutrophils	Phosphorus	12 D to 30 D	Inhibition of superoxide production	Chirumbolo and Bellavite 1993
Wheat germination	Arsenic Silver nitrate	26 D (10^{-45})	Protect from toxicity Enhances growth	Betti 1997/2015 Pongratz 1998
Rat neurons	Glutamate	$10^{-18} \rightarrow 10^{-30}$	Protection from glutamate toxicity	Jonas et al., 2001
Neurocytes	Cycloheximide	10^{-27}	Increases viability	Marotta 2002
Bacteria	Arsenicum	30CH	Protects from toxicity	Das et al 2011, De et al 2012
Neurocytes	Gelsemium s.	2-30 CH	Prevalent gene down-regulation	Marzotto 2014, Olioso 2014
Colon cancer cells	Ruta grav.	MT-30CH	Decrease viability, apo-ptotic gene expression	Arora and Tandon 2015

Bernard Poitevin

One of the first «homeopathic» papers in top journals

Br. J. clin. Pharmac. (1988), **25**, 439–444

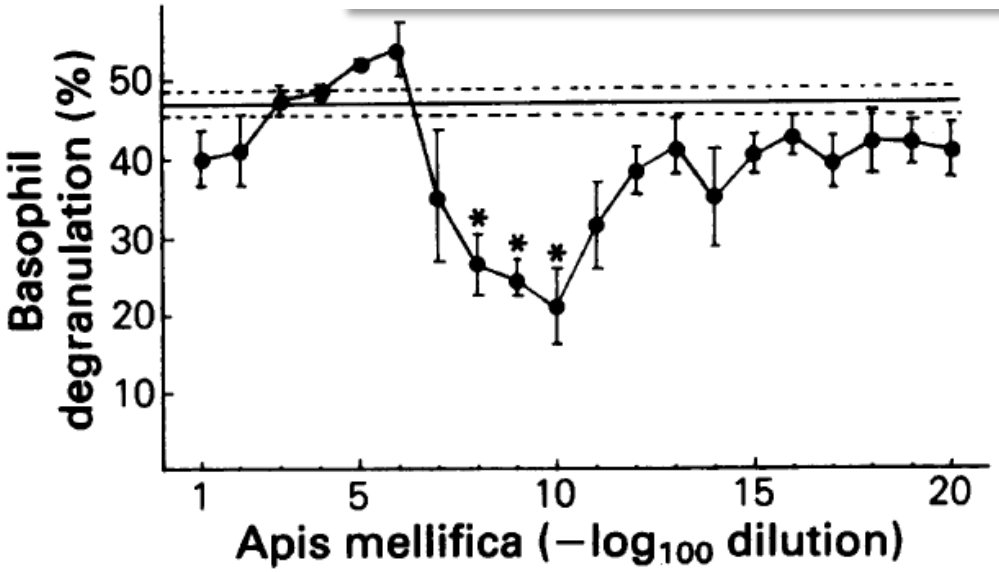
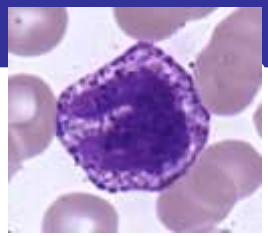


Figure 1 Basophil degranulation induced by 1.66×10^{-9} M (final concentration) anti-IgE antibody in the presence of serial dilutions of Apis mel from 1 to 20 Apis mel. Control degranulations in the presence of HEPES-buffered Tyrode's alone or the dilution corresponding to 9 Apis mel without adding Apis mel in the starting solution were 47.1 ± 1.0% and 46.5 ± 1.6% respectively (mean ± s.e. mean, $n = 4$). Control numbers were pooled in the figure (⁼⁼⁼⁼⁼, mean ± s.e. mean, $n = 8$).* $P < 0.02$.

EFFECT OF HISTAMINE HIGH DILUTIONS ON BASOPHIL "DEGRANULATION"

Philippe Belon



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Inflammation Research

Inhibition of human basophil degranulation by successive histamine dilutions: Results of a European multi-centre trial

P. Belon[1], J. Cumps[2], M. Ennis[3], P.F. Mannaioni[4], J. Sainte-Laudy[5], M. Roberfroid[6] and F.A.C. Wiegant[7]

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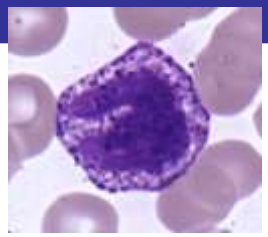
[7] University of Utrecht, Department of Molecular Cell Biology, P.O. Box 80.056, NL-3508 TB Utrecht, The Netherlands

Laboratory	Control (% degranulation)	Histamine (% degranulation)	Number	p
1	45.8	36.5	123	0.0002
2	50.2	47.5	312	0.065
3	51.6	47.4	183	0.024
4	47.8	35.7	154	≤ 0.0001
All	48.8	41.8	772	≤ 0.0001

Statistical comparisons were made using MANOVA.

Table 1. Comparison of percentage degranulation induced by anti-IgE (0.04 µg/ml) in the absence and presence of histamine dilutions (15th–19th centesimal dilutions).

REPLICATION EXPERIMENTS OF HIGH-DILUTION EFFECTS



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

Inflammation Research

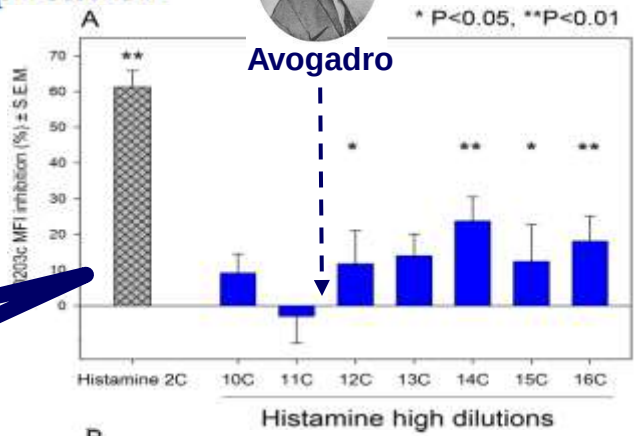
ORIGINAL RESEARCH PAPER

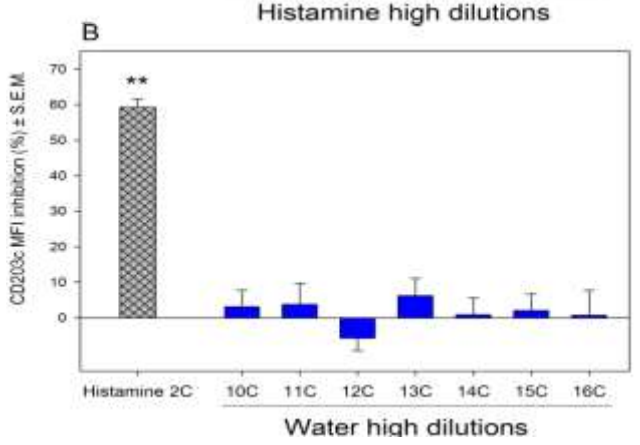
Inhibition of CD203c membrane up-regulation in human basophils by high dilutions of histamine: a controlled replication study

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

Receive 009

Avogadro



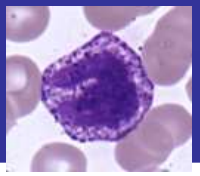


Note:

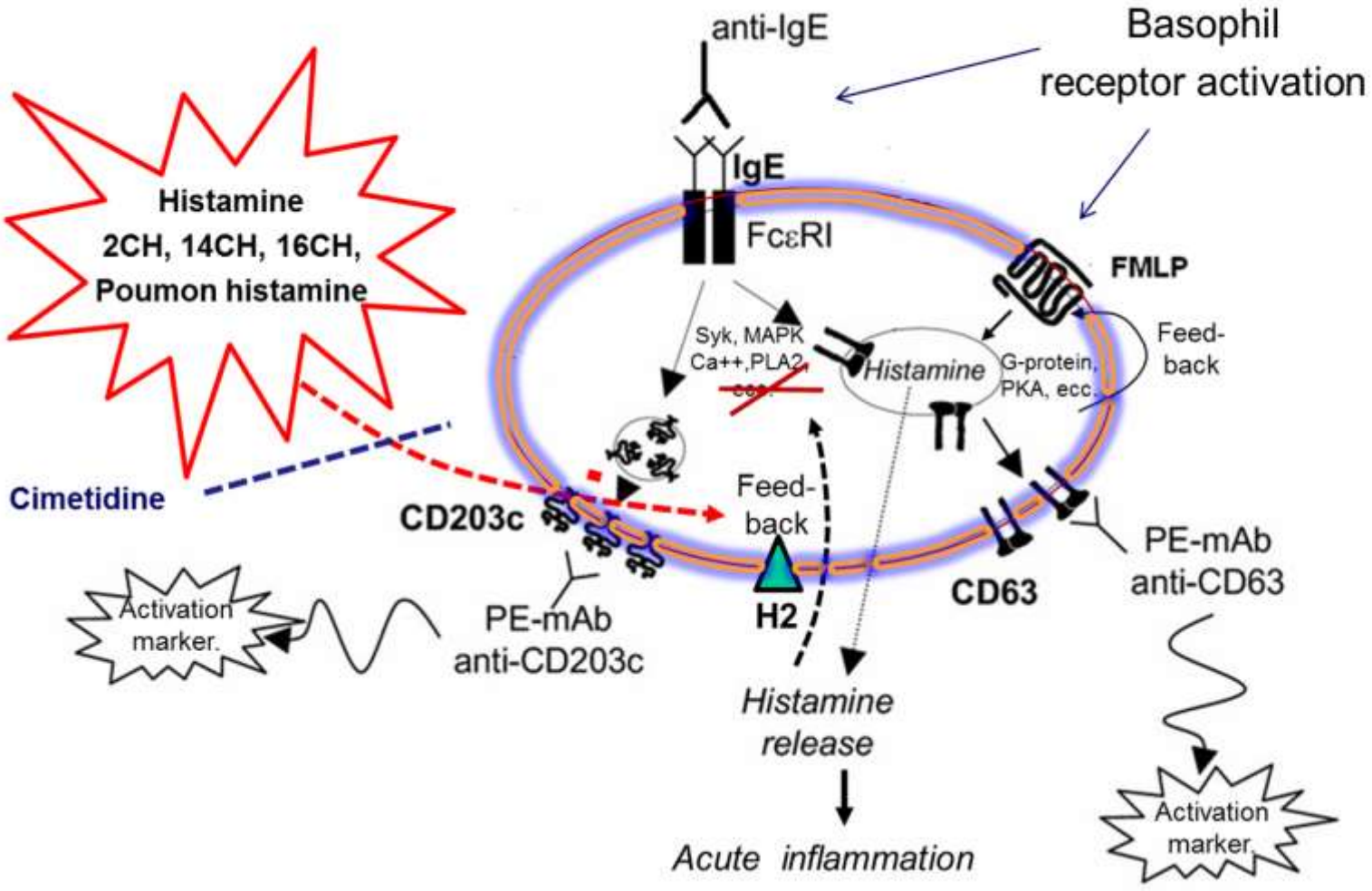
No inversion of effects

No hormesis

Striking non-linearity

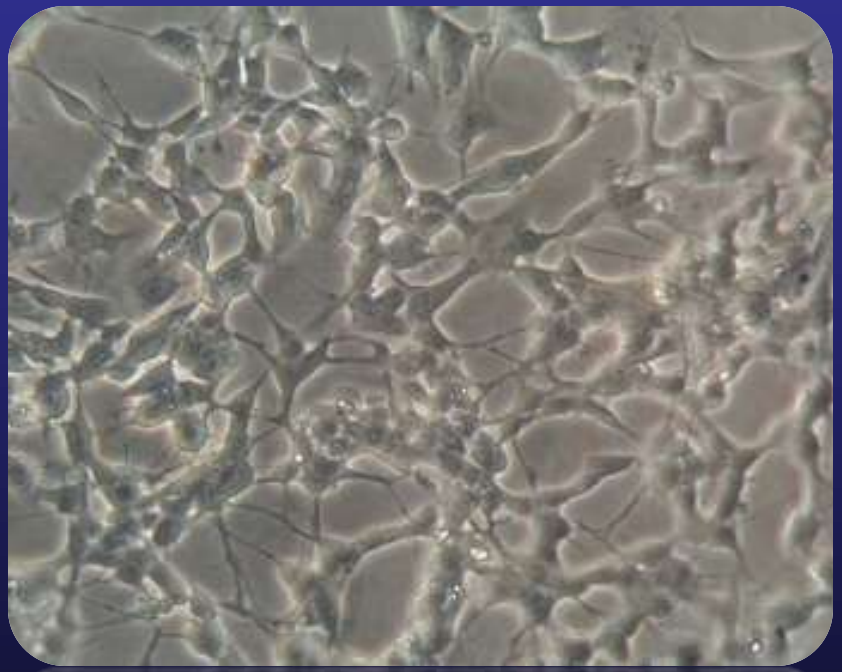


MODEL OF THE HISTAMINE ACTION ON BASOPHILS AND MAST CELLS

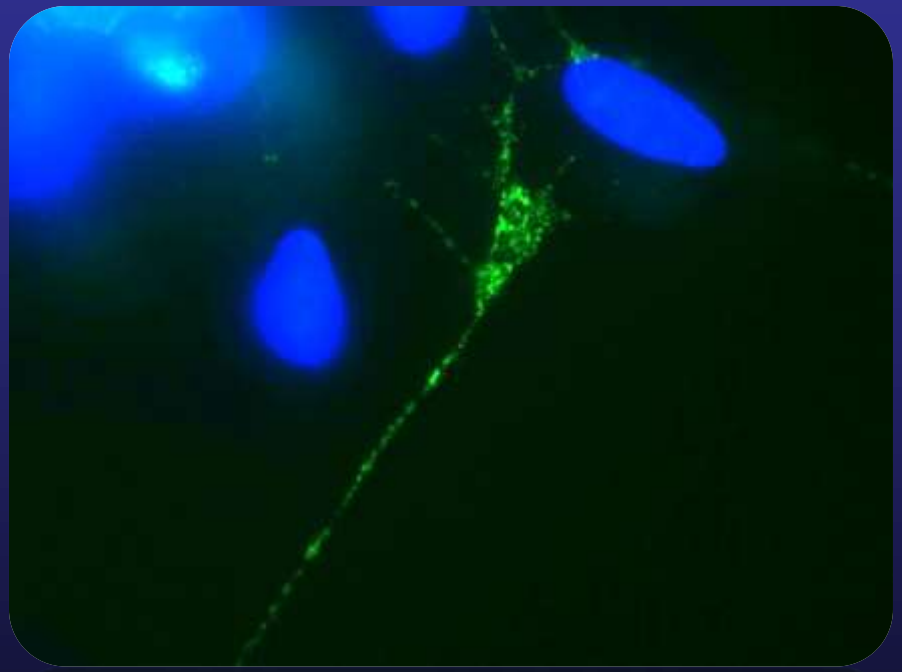


Gelsemium s. in a neuronal model

SH-SY5Y neurocytes-human neuroblastoma cells



Inverted microscope image



Confocal immunofluorescent image

BMC-Complementary Alternative Medicine March 2014

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

while 7 genes were overexpressed

Many of these genes belong to:

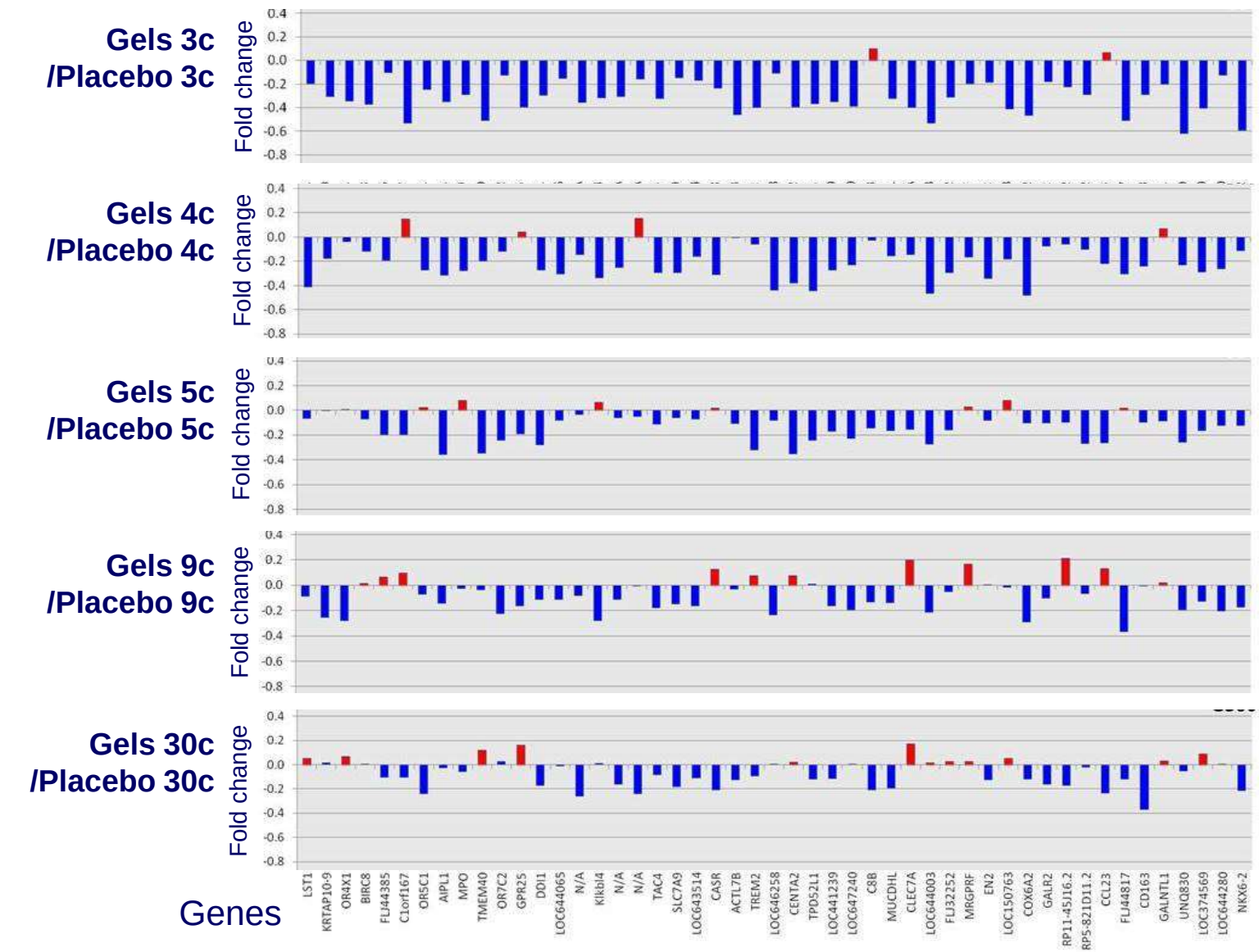
- neuropeptide/receptor systems
- calcium signalling
- G-protein coupled transduction systems
- inflammatory pathways

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* increasing dilutions/dynamizations on the expression of 49 Gels C2-down-regulated genes



	N. Genes UP/DOWN	P (Fisher)
Gels 3c /Placebo 3c	2↑ 47↓	<0.001
Gels 4c /Placebo 4c	3↑ 42↓	<0.001
Gels 5c /Placebo 5c	3↑ 38↓	<0.001
Gels 9c /Placebo 9c	9↑ 30↓	<0.01
Gels 30c /Placebo 30c	7↑ 27↓	<0.01

Recent evidence of Homeopathy and genome analysis

	Potencies	Cell type	Effect	REF
Carcinosinum	MT, 30C, 200C	DLA cells	**↑ specific gene expression (p53 pro-apoptotic)**	**(Sunila et al. 2009)**
Arsenicum alb.	30C	Saccharomyces cerevisiae, E. coli	**↑ Resistance to arsenicum toxicity ↓↑ expression of specific genes (apoptotic, stress response proteins)**	**(Das et al. 2011; De et al. 2012 of Khuda-B.group)**
Carcinosinum, Hydrastis, Ruta or Thuja	200C	DLA cells	**↑ Apoptosis , ↓↑ Gene expression (whole genome analysis)**	**(Preethi et al. 2012)**
Gelsemium s.	2C, 3C, 5C, 9C, 30C	Human neurocytes SHSY5Y	**7 genes ↑ 49 genes ↓ expression (whole genome analysis) ↓ gene expression (RT-Array, 2C)**	**(Marzotto et al. 2014; Olioso et al. 2014)**
Apis mellifica	3C, 5C, 7C	Human prostate RWPE-1	**↑↓ expression of different groups of genes (whole genome analysis)**	**(Bigagli et al. 2014)**
Rhus tox.	30X	Primary cultured mouse chondrocytes	**↑ specific gene expression (COX-2), ↓ specific gene expression (collagen II; de-differentiation role)**	**(Huh et al. 2013)**
Arsenicum alb.	45X	Arsenic-intoxicated wheat seeds	**↑ Germination ↓ Gene expression levels**	**(Marotti et al. 2014)**
Condurango	30C	H460-non-small-cell lung cancer cells	**↓↑ expression of specific genes (apoptotic), ↑ Apoptosis, oxidative stress, mitochondrial depolarization**	**(Sikdar et al. 2014)**

Homeopathy and gene expression

DNA gene expression is sensitive to:

→Low energy information (Montagnier studies)

→High homeopathic dilutions

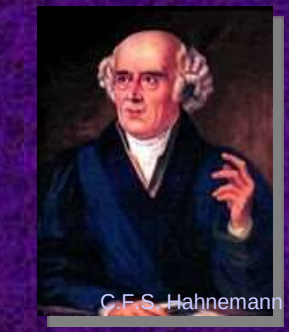
→Bioelectromagnetics

→Water clusters

The rapid development of new high-throughput technology platforms provides a methodological basis for deep understanding the action mechanisms and targets of homeopathic remedies.

In future: Help in prescription??

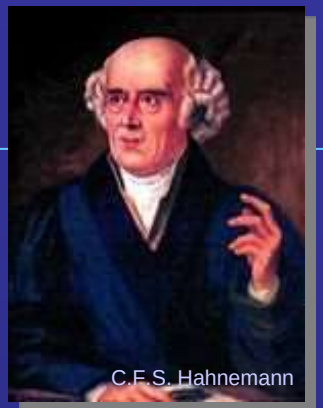
CUTTING EDGE RESEARCH IN HOMEOPATHY
ROME 2015



Basic research on homeopathic principles

1. Introduction (motivation)
2. Studies in animal and plant models
3. In vitro laboratory studies
4. Perspectives

CUTTING EDGE RESEARCH IN HOMEOPATHY ROME 2015



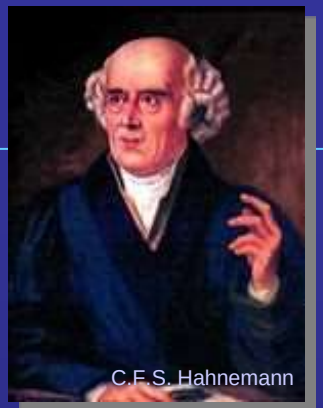
3 major certainties

- The inverse effects of high vs low doses in several cellular, plant and animal models (classic hormesis, Arndt-Schulz, initial value of Wilder)
- The effects of different substances in high dilutions (beyond Avogadro) described in many different models and many different laboratories: no placebo
- Action on cell receptors and on gene expression

3 major uncertainties

- The inter-experiment and inter-laboratory reproducibility, seasonal effects, etc. An “intrinsic” feature of high dilutions (non-linearity, chaos theory)?
- The nature of the “physical” state of the highly diluted solutions
- The transfer of information from triturations to liquid and from liquid to granules

CUTTING EDGE RESEARCH IN HOMEOPATHY
ROME 2015



Future tasks

- Further development of laboratory models for
  a) *high dilutions/dynamizations* and
  b) *similia principle* (opposing effects in normal and stressed systems)
- Identification of variables and critical factors in reproducibility
- Evaluation of different preparations (liquid, granules, alcohol) and different dynamization procedures
- Integration of experimental models from molecules to humans for specific relevant remedies (“from bench to bedside”)

Scientific research on high dilutions of Phosphorus

- 1975-84 ➢ 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].
- 1987 ➢ The mortality of rats treated with lethal doses of α-amanitine is significantly slowed by treatment with 15c dilutions of *Phosphorus* [Guillemain *et al.* 1987].
- 1993 ➢ Protective effect of *Phosphorus* 30c on fibrosis of the liver caused by chronic administration of CCl4 in rats [Palmerini *et al.* 1993]
- 1993 ➢ *Phosphorus* and *Magnesia phosphorica* (dilutions greater than 15x) decrease free radical production by human granulocytes [Chirumbolo *et al.* 1993]
- 2007 ➢ Phosphorus 1M reduces the incidence of 3-methylcholanthrene-induced sarcomas and also increase the life span of mice harboring the tumours [Kumar et al. 2007].
- 2008 ➢ In rats, Phosphorus 12x shows a protective action on the mortality by T. cruzi infection (Chagas disease) [de Almeida *et al.* 2008]
- 2011 ➢ Homeopathic Phosphorus (P) (9c) improved growth and yield of essential oil of Verbena gratissima, a plant native to Brazil [Santos *et al*. 2011]. No effects on Lemna gibba where Arsenicum acted[Jager et al. 2011]
- 2014 ➢ Phosphorus high dilutions (15c and 200c) was successfully used in 2 patients with fulminant hepatic failure from Amanita phalloides poisoning [Frass *et al.* 2014]

The research ways: Evidence and Plausibility

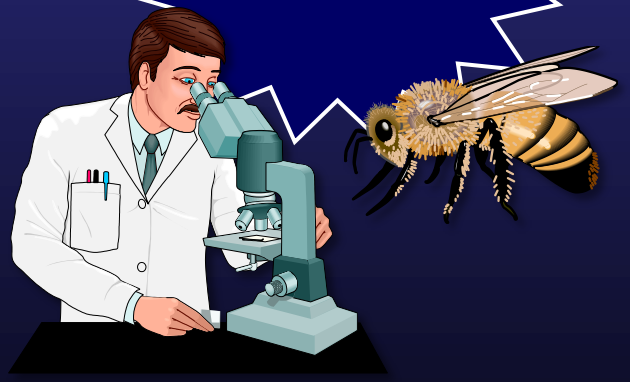
CLINICAL RESEARCH

«EVIDENCE»

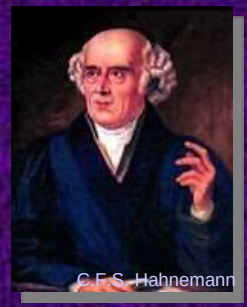
Homeopathy acceptation and progress

«PLAUSIBILITY»

BASIC RESEARCH



CUTTING EDGE RESEARCH IN HOMEOPATHY
ROME 2015



SAPERE AUDE!

(DARE TO KNOW! -必须知道的勇气！)

Orazio (*Epistole* I, 2, 40)