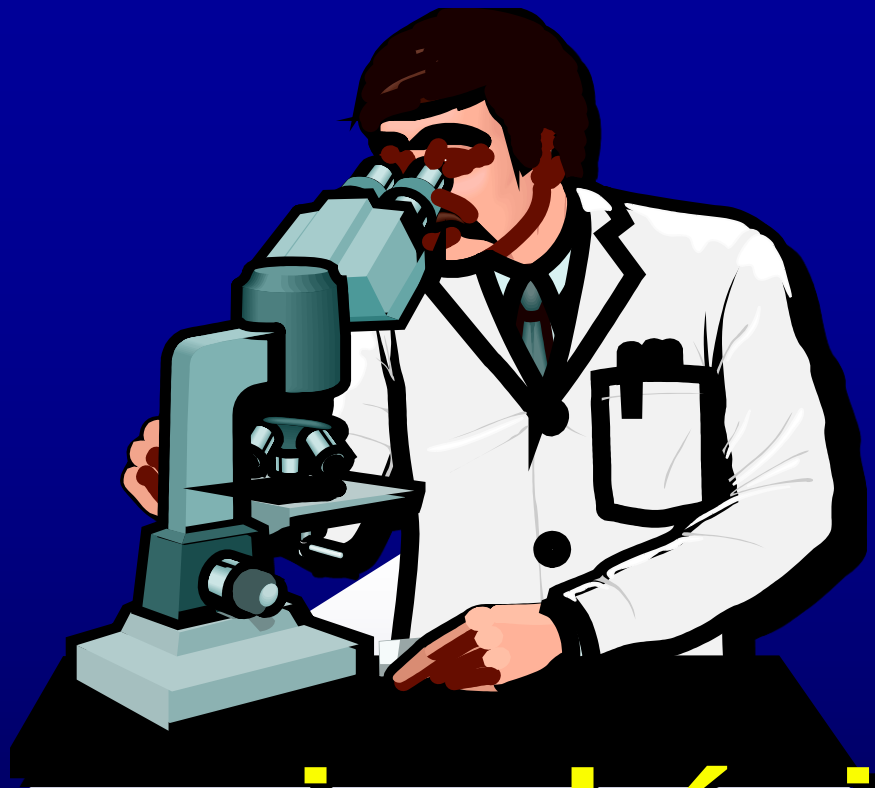
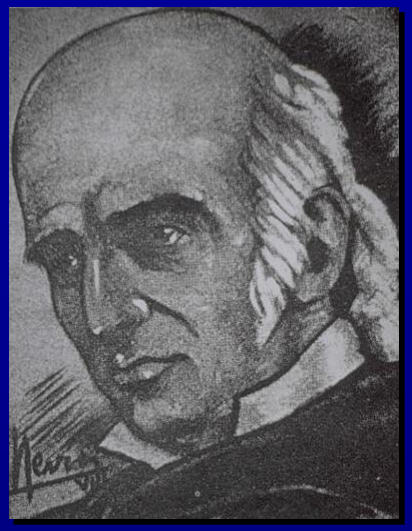




Pesquisa básica e homeopatia - part 1

Basic research and homeopathy

Paolo Bellavite, MD, Università di Verona, Italia

RESEARCH IN HOMEOPATHY

DOES HOMEOPATHY WORK?

HOW DOES IT WORK?

COULD IT WORK BETTER?

CLINICAL RESEARCH

BASIC RESEARCH

Pesquisa básica e homeopatia- basic research and homeopathy

- Introduction: Basic research and homeopathic principles
- Part 1: Scientific reevaluation of the “similia” principle
- Part 2: The problem of doses/potencies and related questions
- Part 3: Working hypothesis on the action mechanism of homeopathy (→ The homeopathic paradigm)

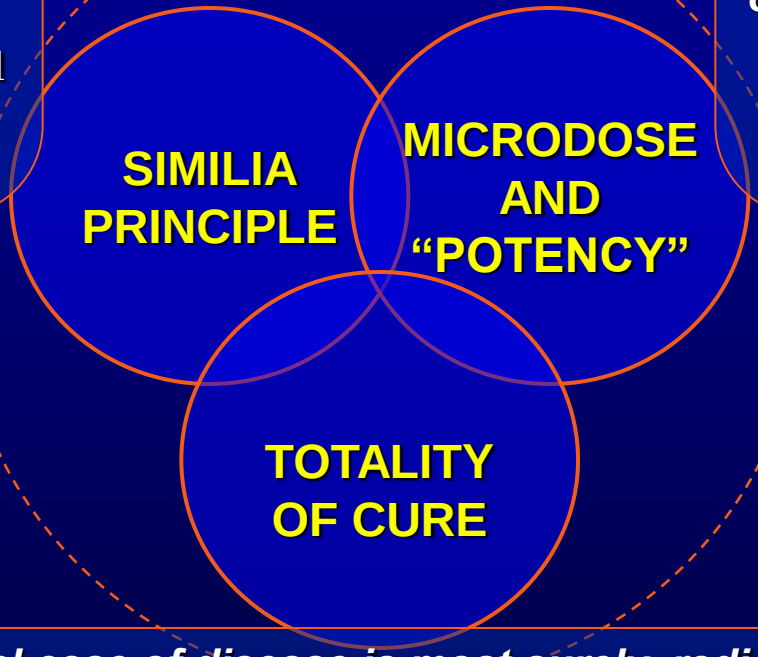
THE MAJOR TENETS OF HOMEOPATHY

"By choosing a remedy for a given natural disease that is capable of producing a very similar artificial disease we shall be able to cure the most obstinate diseases"

S. Hahnemann, Hufeland's Journal 2: 381 (1796)

"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..."

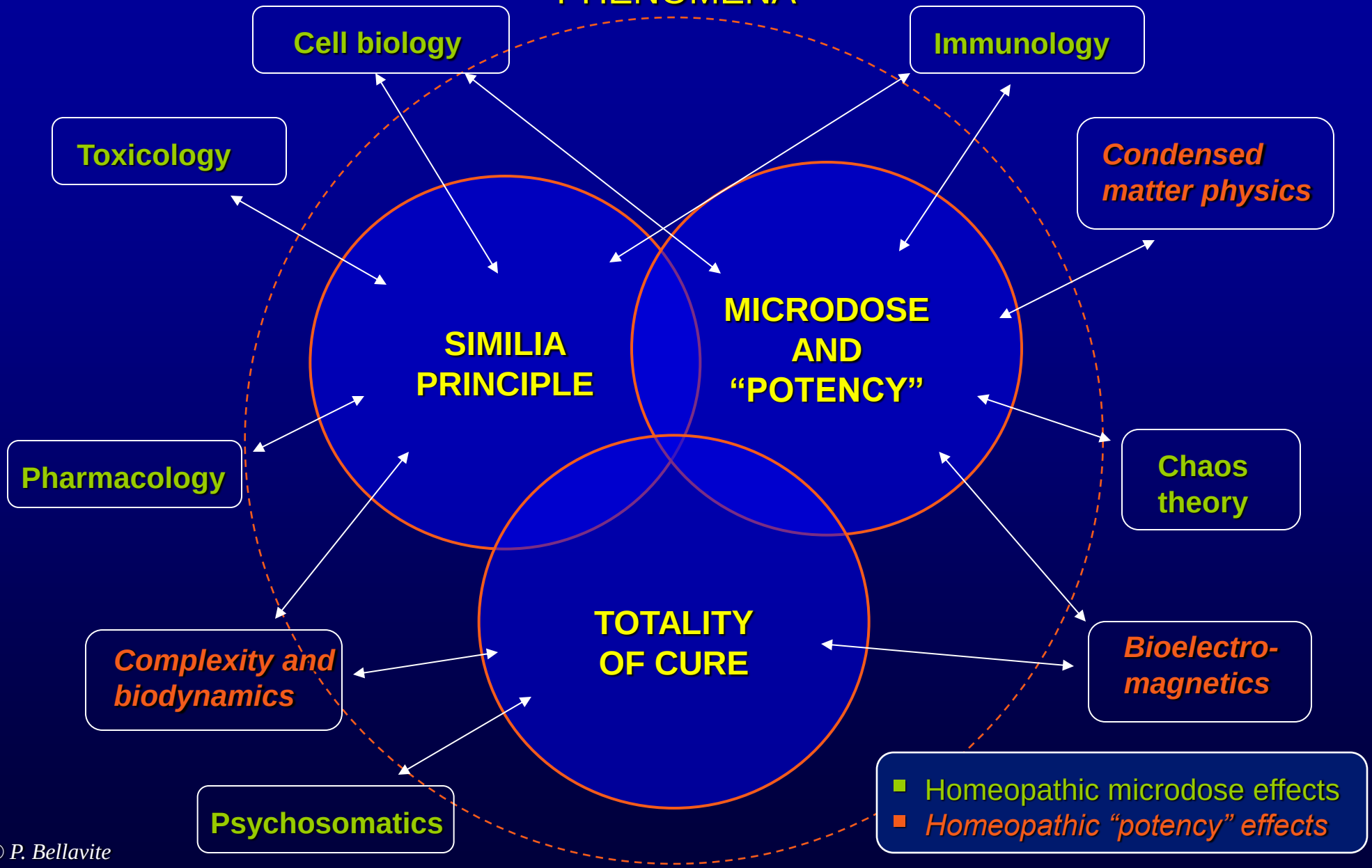
S. Hahnemann, The Organon of Medicine (1820), par 277



"Each individual case of disease is most surely, radically, rapidly and permanently annihilated and removed only by a medicine capable of producing (in the human system) in the most similar and complete manner the totality of its symptoms"

C.F.S. Hahnemann, The Organon of Medicine (1820), par. 27

SCIENCE FIELDS INVOLVED IN THE INVESTIGATION OF HOMEOPATHIC PHENOMENA



The principle of similarity, microdose-mediated homeopathic effects and totality of cure can be investigated and understood independently of the so-called “high dilution” or “high potency” effects

- Historically, the *Similia principle* is the first “law” and the basis of the homeopathic method
- Many homeopathic drugs contain significant amount of active compounds
- In cellular models and in animals, the *Similia principle* has been widely exploited using low-doses of drugs

Pesquisa básica e homeopatia- basic research and homeopathy

- Part 1: Scientific re-evaluation of the “similia” principle

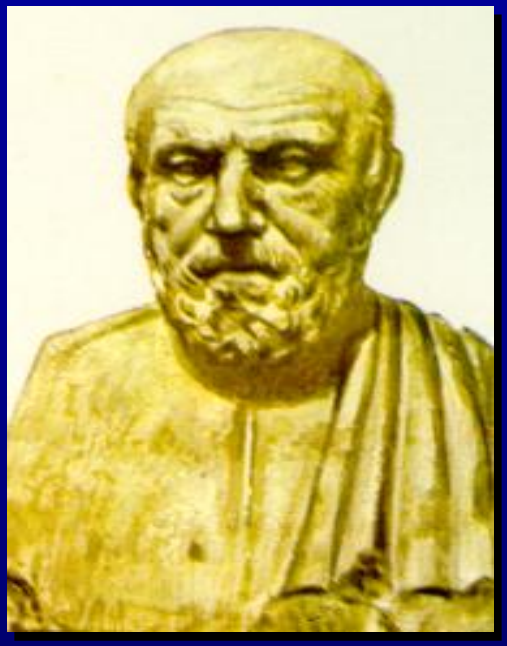
Similia principle

(Principle of Similarity)

when a substance
is able to *induce* a series of symptoms
in a healthy living system
it would be also able under certain circumstances
to *cure* these symptoms
when applied at low doses
(“*similia similibus curentur*”)

"Through the similar the disease develops and through the employment of the similar the disease is healed.
So that which produces urinary tenesmus in the healthy, cures it in disease.
Cough is provoked and healed through the same agent, just as in the case of urinary tenesmus"

Littre's Oeuvres Completes d'Hippocrates, Paris, 1839, 6, 334.



Hippocrates
(460-377 B.C.)

A scientific reevaluation of Similia principle
=
"inversion of effects"

- *Biphasic or polyphasic dose-response effects*
- *Reversal of inhibition during time*
- *Inverse effects in systems at different physiological states*

Bellavite et al., *Br.Hom.J.* 86:73-85, 1997
Bellavite et al., *Medical Hypoth.*, 49: 203-212, 1997
Bellavite et al. *Ann. Ist. Sup. Sanità* 35(4): 517-527, 1999

EXAMPLES OF INVERSE EFFECTS WITH HOMEOPATHIC DILUTIONS

System	Agent	Conventional effect	Inverse/homeopathic effect	Ref.
Basophils	Histamine Apis mellifica	**Pro-inflammatory agents**	**Histamine (up to 60x) and Apis mellifica (10c)**	Poitevin 1988 S.Laudy 1991 Belon 1996-99
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 1993
Rat Mouse	Arsenic trioxide Arsenicum album	**Whole body and liver toxicity**	**Arsenic trioxide (7c and 17c) and Arsenicum album (30c) protect from intoxication and increase Urinary elimination**	Lapp 1955 Wurmser 1955 Cazin 1987 Cazin 1991 Khuda-Bukhsh 1998-2000
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 (30x) inhibit the metamorphosis**	Endler 1991-98

MODELLING THE SIMILIA PRINCIPLE

- Cells

- Hormesis (stimulation of growth by low doses of toxic compounds or radiations)
- Heat shock proteins
- Gating theory (cyclic AMP)

- Whole organism

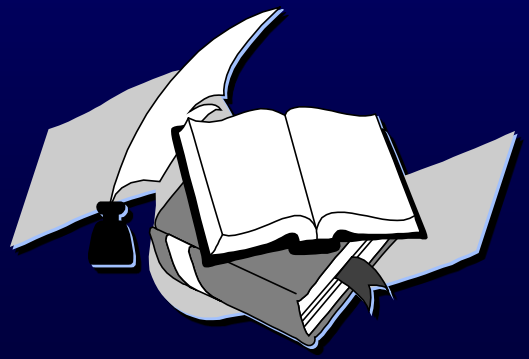
- Immune network and tolerance (animal & humans)
- Chaos and attractors
- Neuroendocrine feedback regulation

- Unifying model

- Regulation of stressed homeostatic networks (→ the homeopathic paradigm)

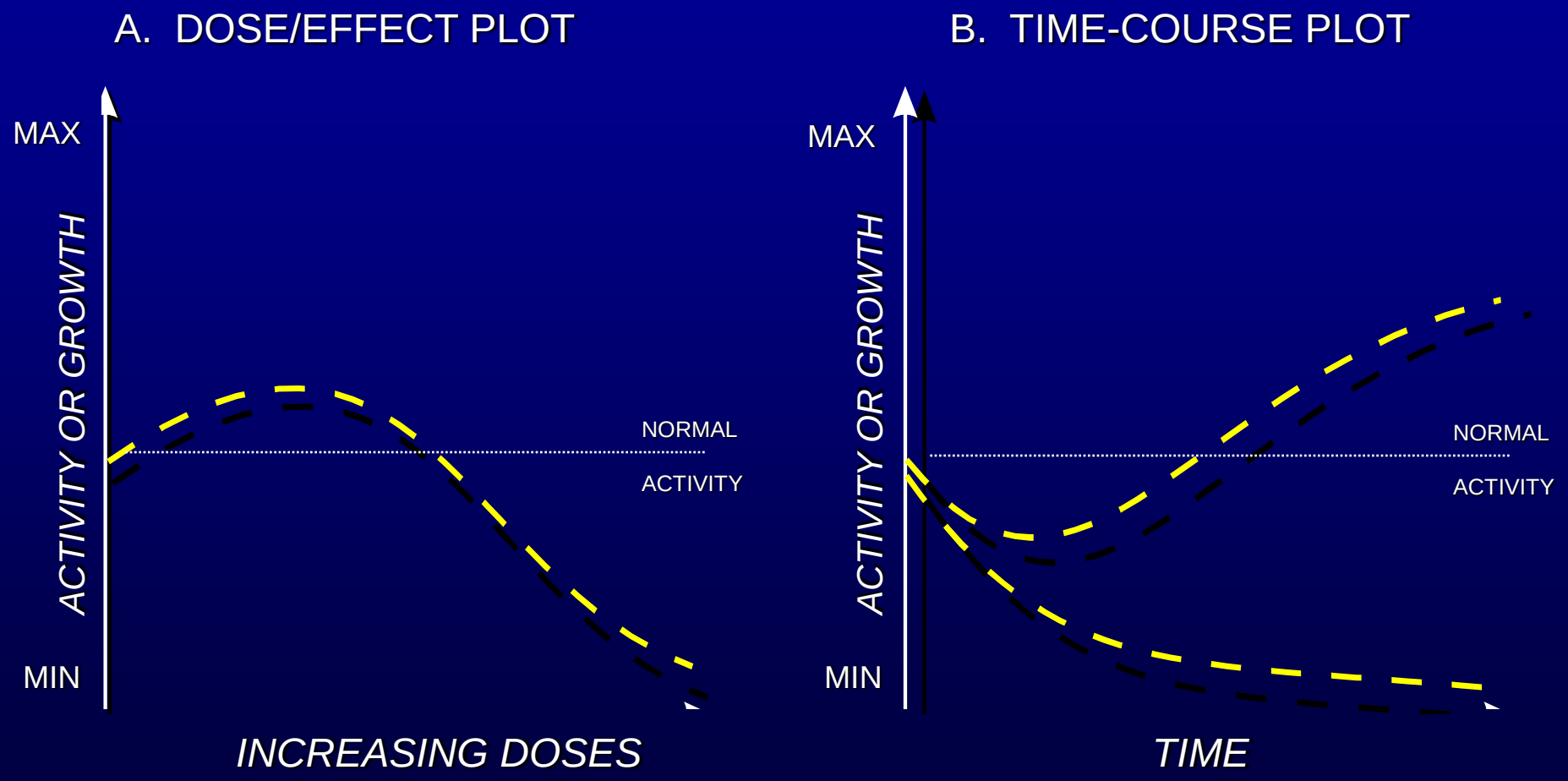
The “Arndt-Schulz law”

“Weak stimuli slightly accelerate vital activity, medium strong stimuli raise it, strong ones suppress it and very strong ones arrest it”



H.Schulz,
Arch fuer Physiol 1888; 42: 517-541

“Hormetic” effects (stimulation by low doses of toxic compounds)

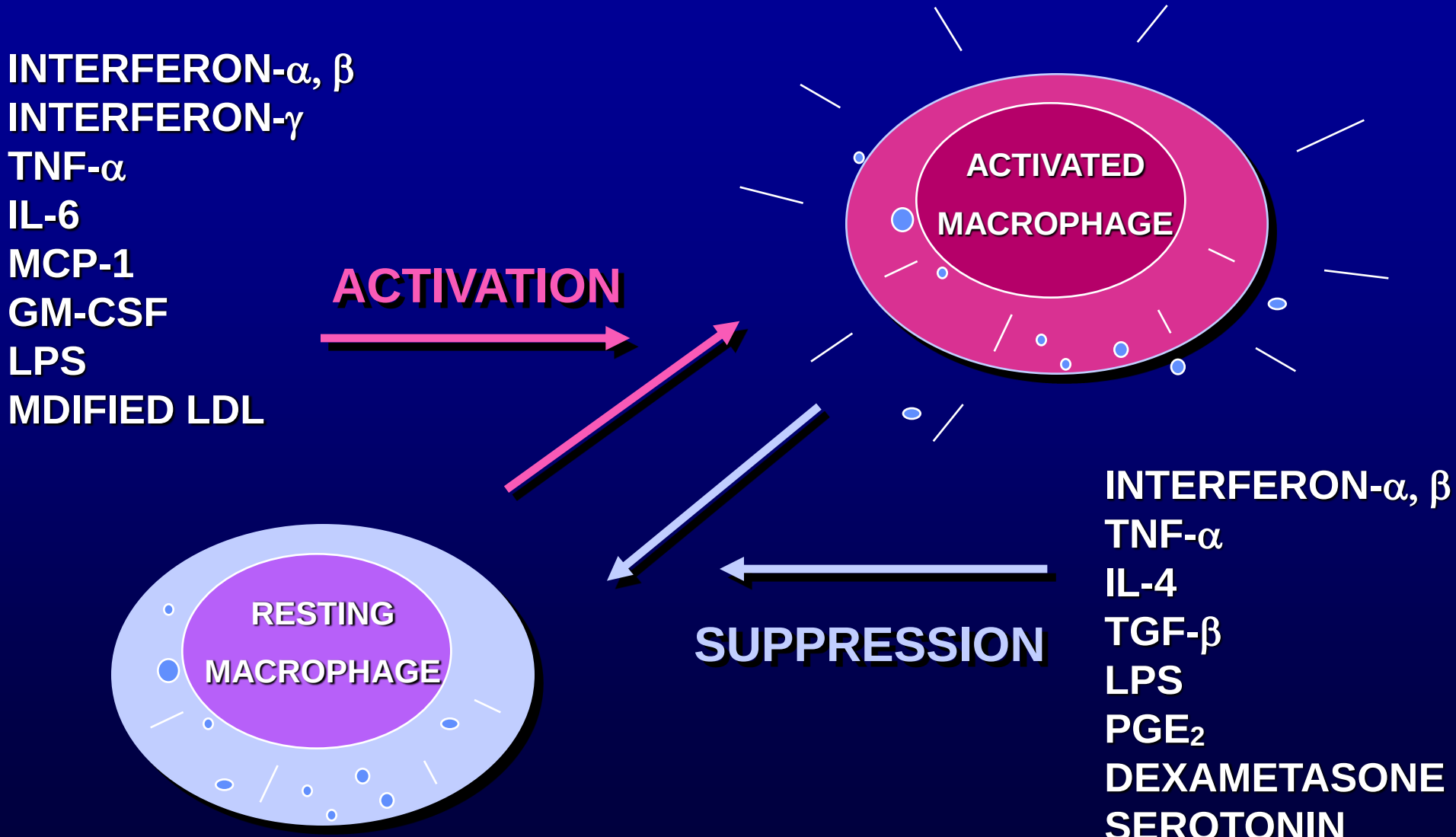


EXAMPLES OF INVERSE EFFECTS IN LABORATORY SYSTEMS

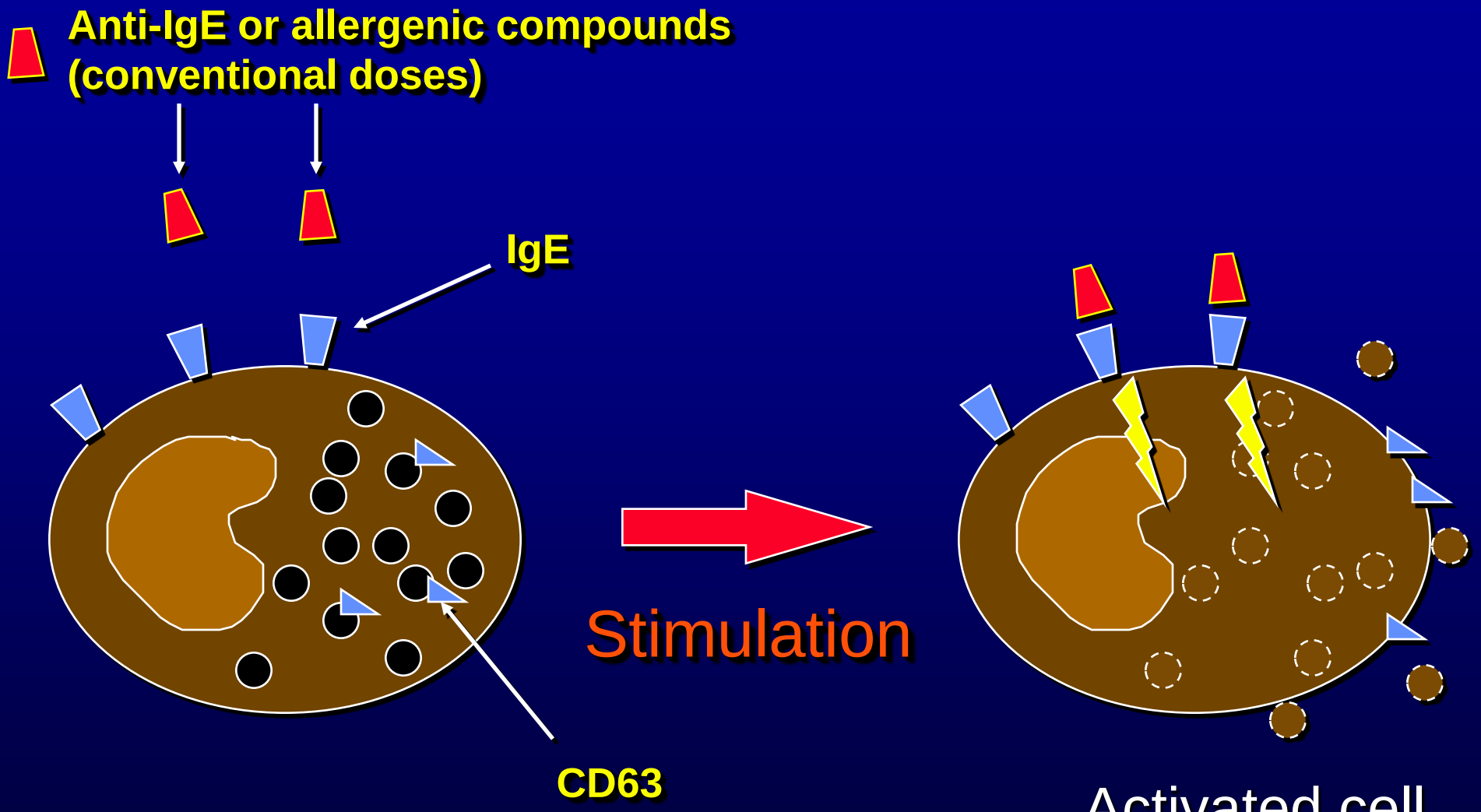
System	Agent	First effect	Inverse effect	Ref.
Yeast	Heavy Metals	**Block growth**	**Low doses increase growth**	Schulz 1988 Martius 1923 Stebbing 1982
Fibroblasts Wheat	Arsenite Cadmium	**Cell toxicity**	**Low doses protect from toxicity or stimulate DNA synthesis**	vanWijk 1995 vanWijk 1997 V.Zglinicki 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

INVERSE EFFECTS OF BIOLOGICAL COMPOUNDS ON MACROPHAGES

(From: Inflammation, Raven Press, 1992. Gallin et al. ed.)

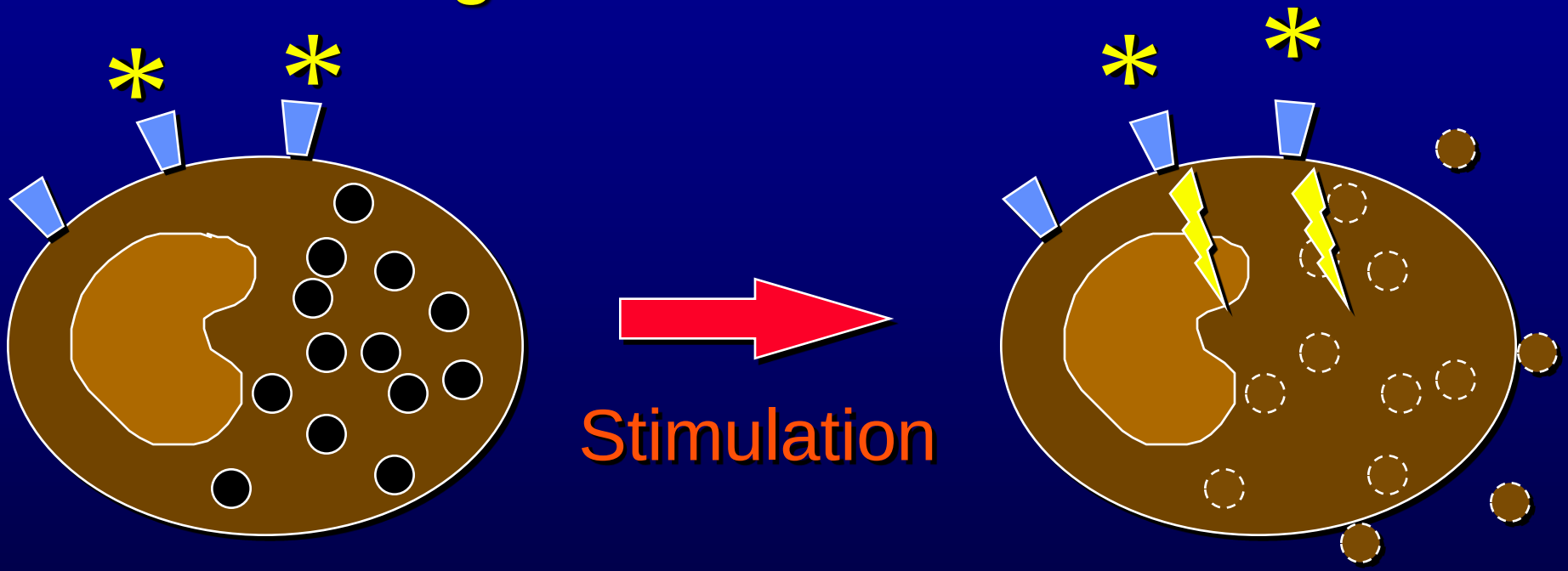


BASOPHIL ACTIVATION



THE FAMOUS EXPERIMENT OF BENVENISTE (DAVENAS ET AL., NATURE1988)

* Ultra-high dilution (up to 10^{-120} Moles/L) of **Anti-IgE**



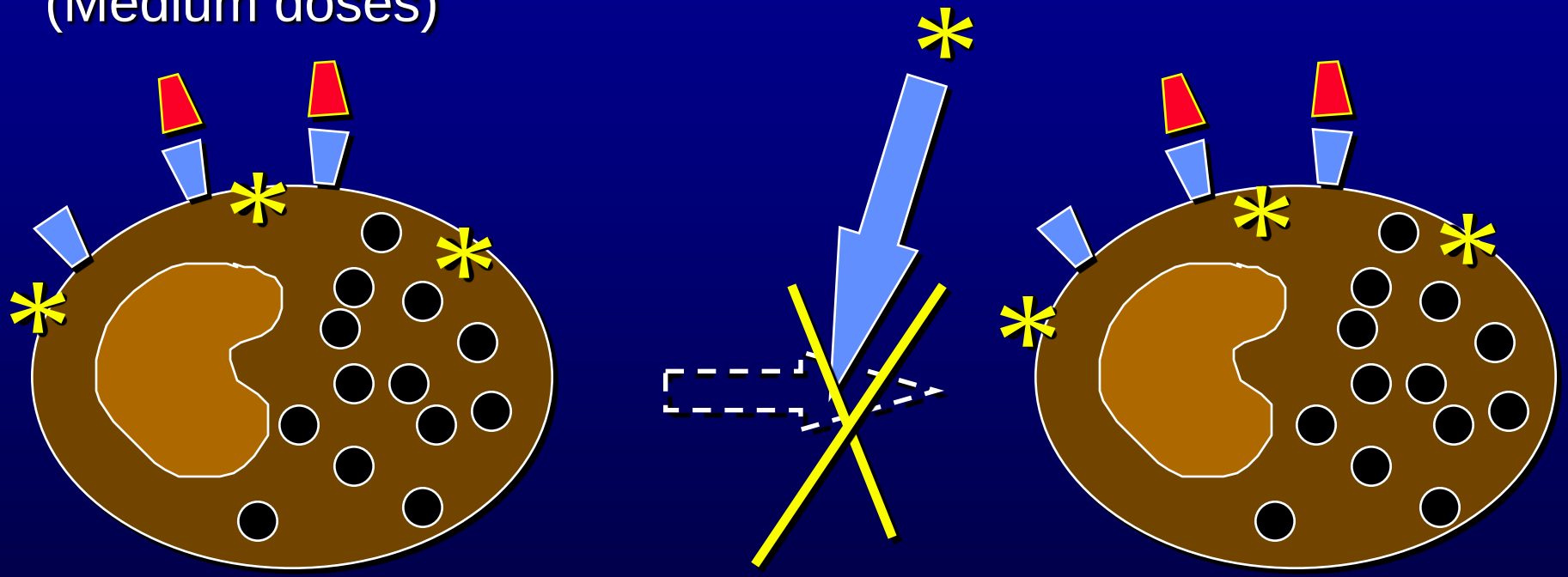
Resting cell

Activated cell

EXPERIMENTS OF POITEVIN ET AL. (BR. J. CLIN. PHARM. 1988)

Homeopathic drugs
LUNG HISTAMINE (5CH, 15 CH)
APIS MELLIFICA (9CH)

Anti-IgE
(Medium doses)



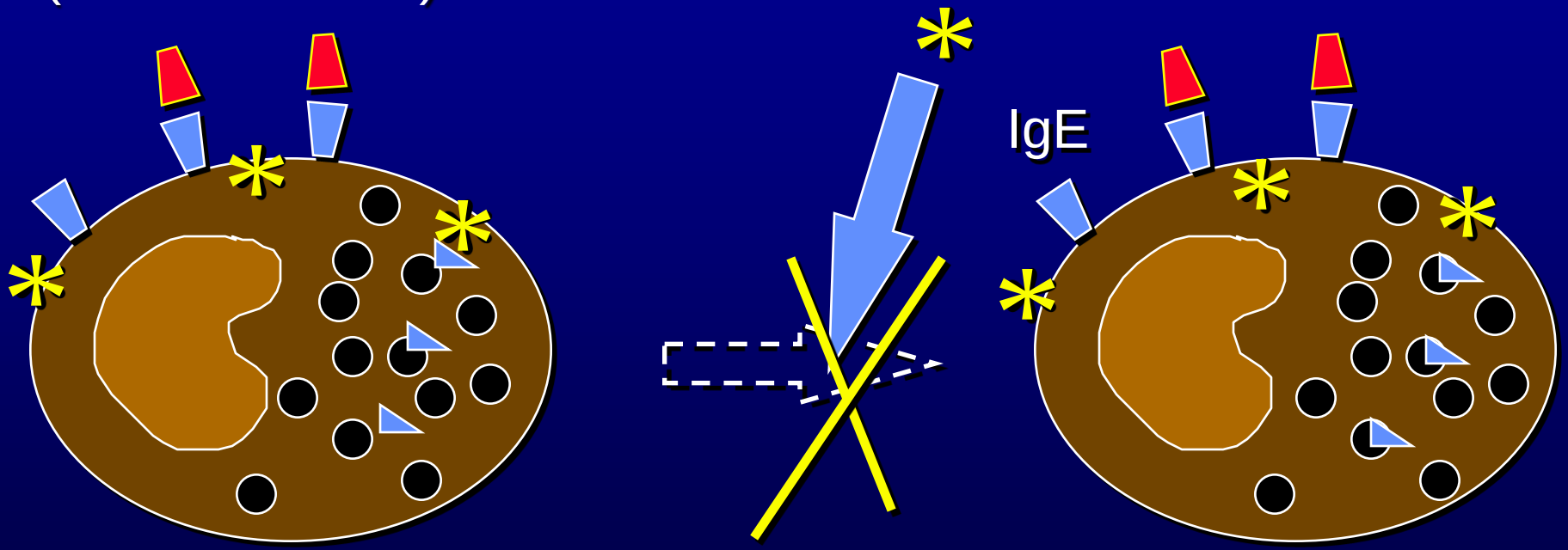
Resting cell

Lack of response
to Anti-IgE

EXPERIMENTS OF SAINTE LAUDY, BELON ET AL. (1989-1999)

Anti-IgE
(Medium doses)

Ultra-high dilution
of **Histamine**



Resting cell

Lack of response
to Anti-IgE

Investigations on complex responses of neutrophils to bacterial products

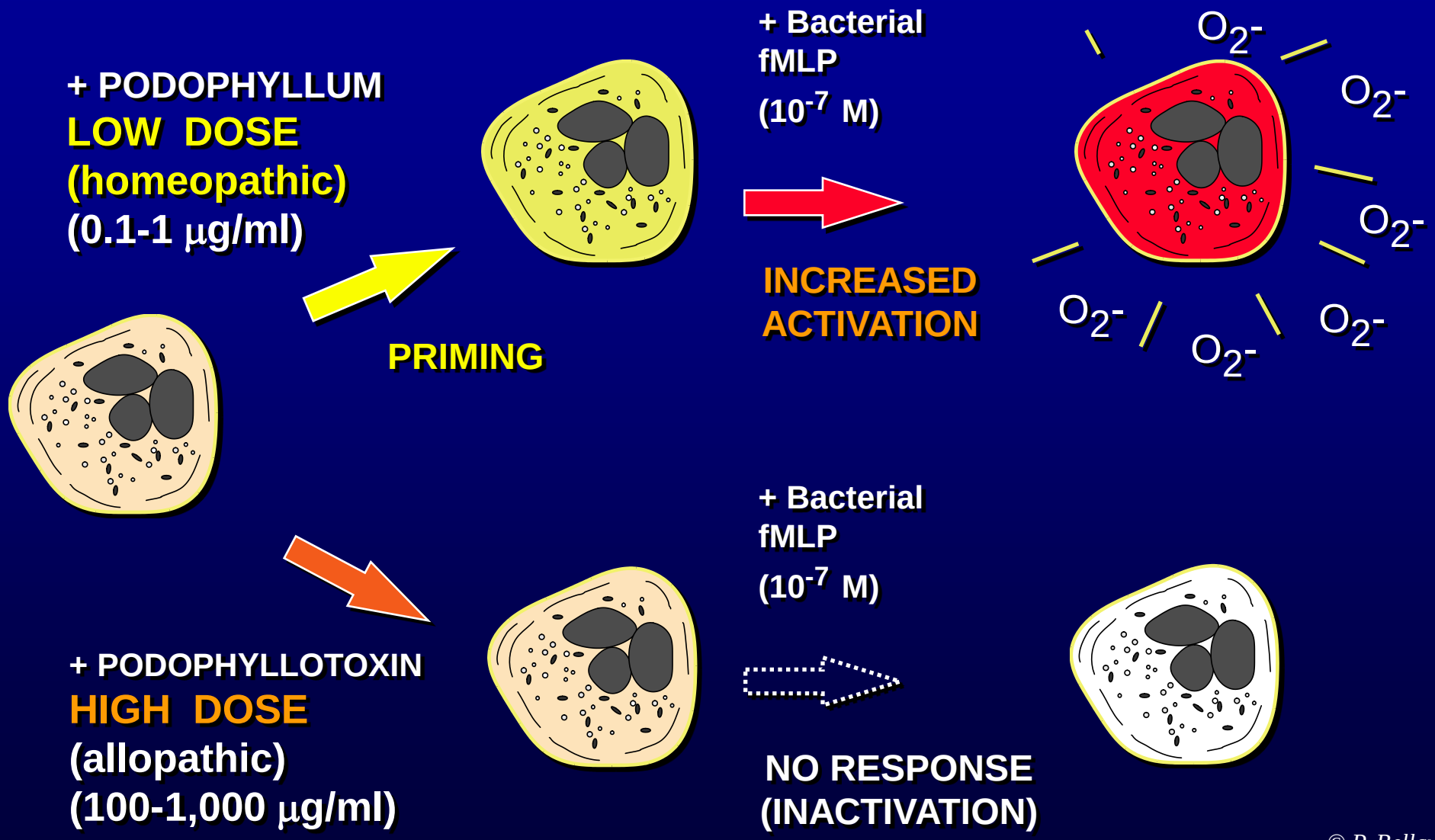
- Inverse effects of different doses
- Homologous priming and desensitization

Hormesis

is a special application of the similia principle at the biological and physiopathological level, but it does not represent "the" explanation of homeopathic effects, which may have further and more complex implications at the level of whole human organism.

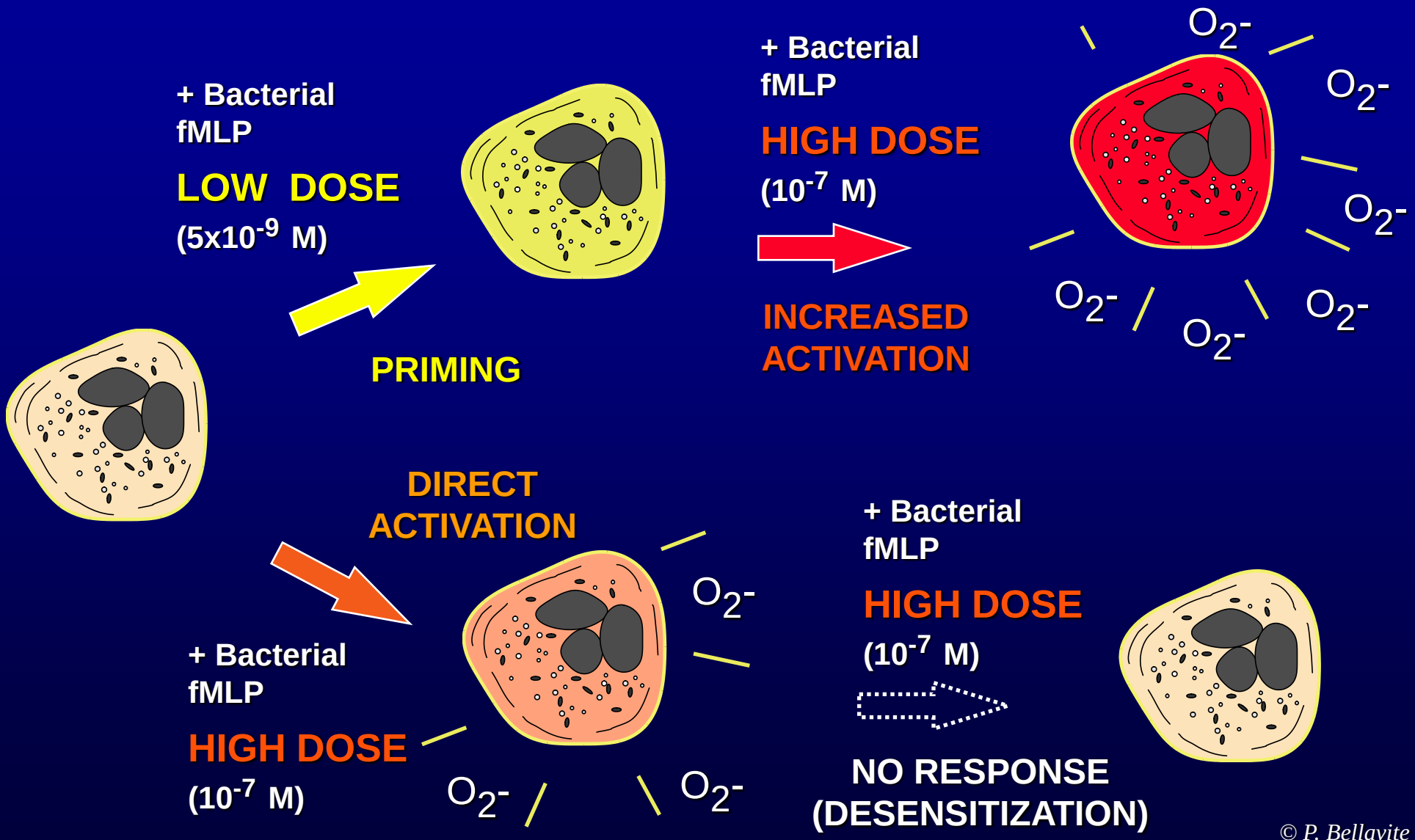
Dual effects of podophyllum on human neutrophils

(Data from Chrumbolo and Bellavite, *Brit. Hom. J. 86: 16-26, 1997*)



Priming and desensitization of human neutrophils

(Data from Bellavite et al., *Cell Biochem. Funct.* 11: 93, 1993)



Priming

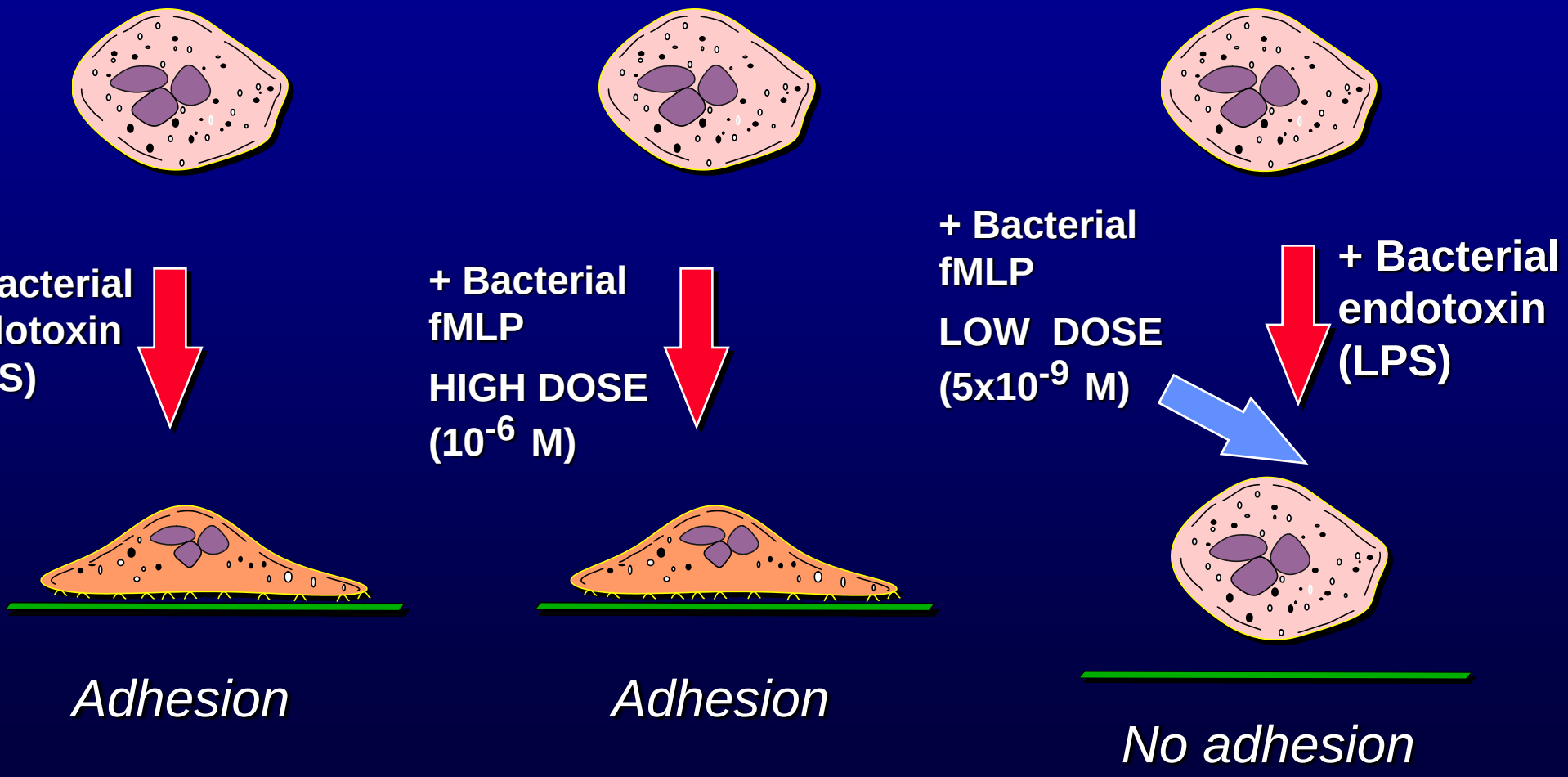
is a state of hyperactivation in response to a given stimulant, which characterizes a cell or a system after it has received pretreatment with low doses of the same stimulant (homologous priming) or of other stimulants of a different type (heterologous priming)

Desensitization

is a state characterized by lack of responsiveness to a given stimulus after the cell or the organism have received pretreatment with the same stimulant (homologous desensitization) or with different stimulants (heterologous desensitization)

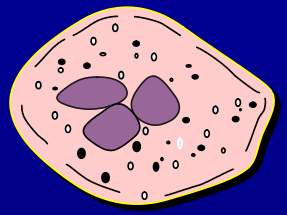
A typical example of inverse effects of different doses of a stimulant (FMLP) on the adhesion of human neutrophils

(Data from Bellavite et al., *Cell Biochem. Funct.* 11: 231, 1993)

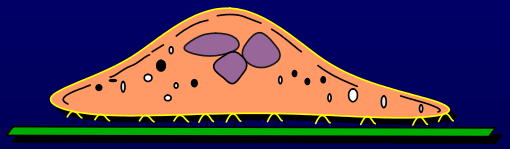


Inverse effects of different doses of fMLP on the adhesion of inflammatory human neutrophils

(Data from Bellavite et al., *Inflammation.* 18: 575, 1994)



In vivo skin inflammation

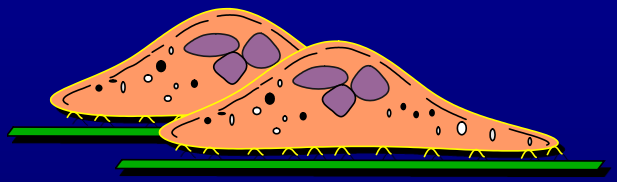


Adhesion

+ Bacterial fMLP

HIGH DOSE

(10^{-6} M)

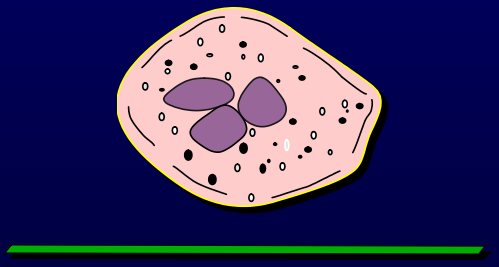


Increased adhesion

+ Bacterial fMLP

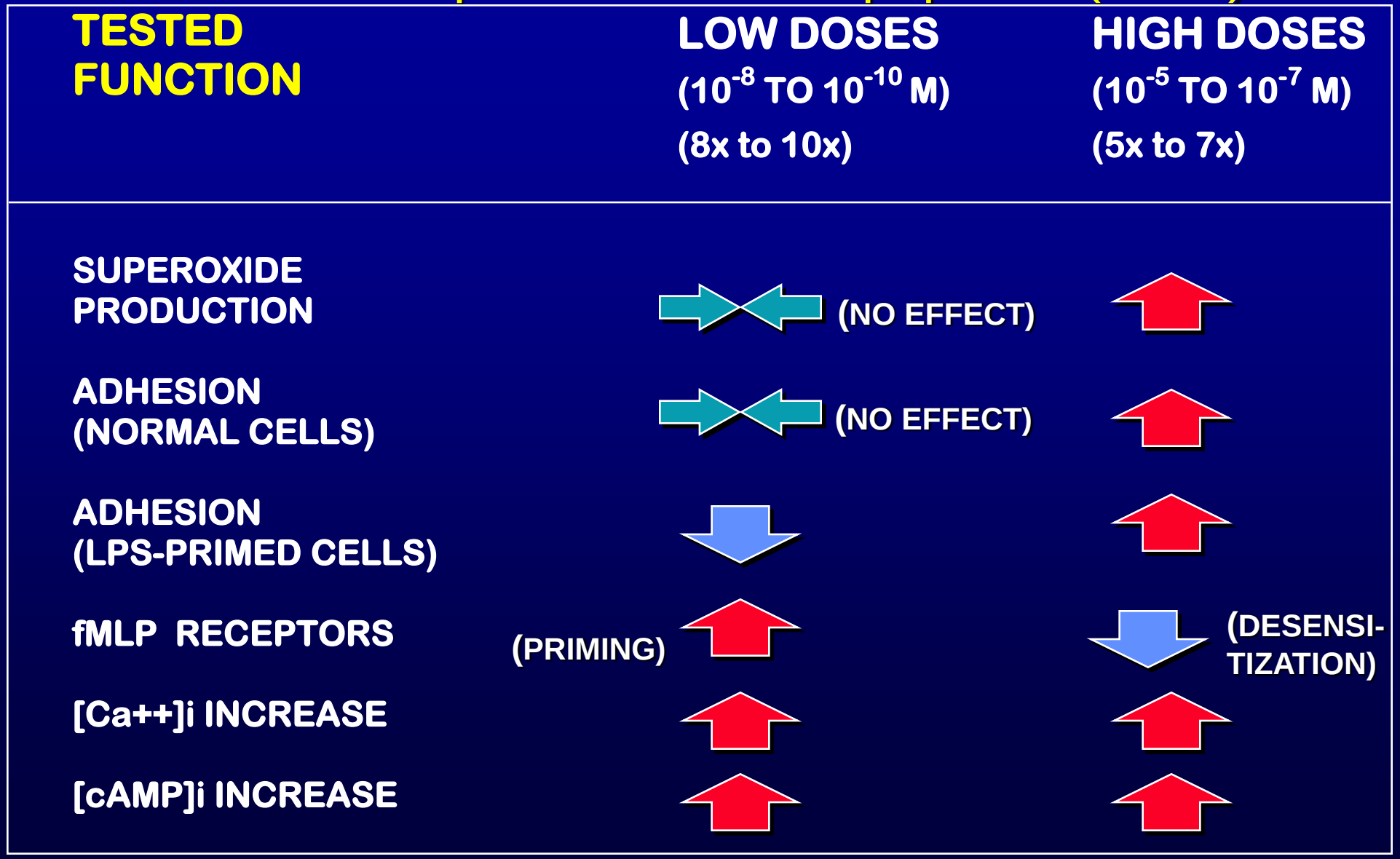
LOW DOSE

($5x10^{-9}$ M)



Decreased adhesion

Summary of the dose-dependence of responses of human neutrophils to bacterial peptides (fMLP)



Specificity of the inhibition of adhesion by FMLP in human neutrophils pre-treated with various agents

PRE-TREATMENT	STIMULANT (low doses)	EFFECTS of STIMULANT ADHESION	cAMP
LPS	FMLP	↓	↑
LPS	Concanavalin A	↑	NO EFFECT
LPS	Phorbol esters	↑	NO EFFECT
TNF-α	FMLP	↓	↑
Inflammation	FMLP	↓	↑
Inflammation	Concanavalin A	↑	NO EFFECT

The complexity of *in vitro* regulation of human neutrophils (summary)

- Neutrophils exposed to LOW doses of fMLP are primed to further stimuli, while neutrophils exposed to HIGH doses are desensitized
- Adhesion of NORMAL neutropils is activated by high doses of fMLP, while adhesion of LPS-TREATED neutrophils is inhibited by low doses of fMLP
- Inverse effects can be observed in several (but not all) models, thus the experimental conditions (doses, type of stimulant, cell treatment, cell function) must be carefully set

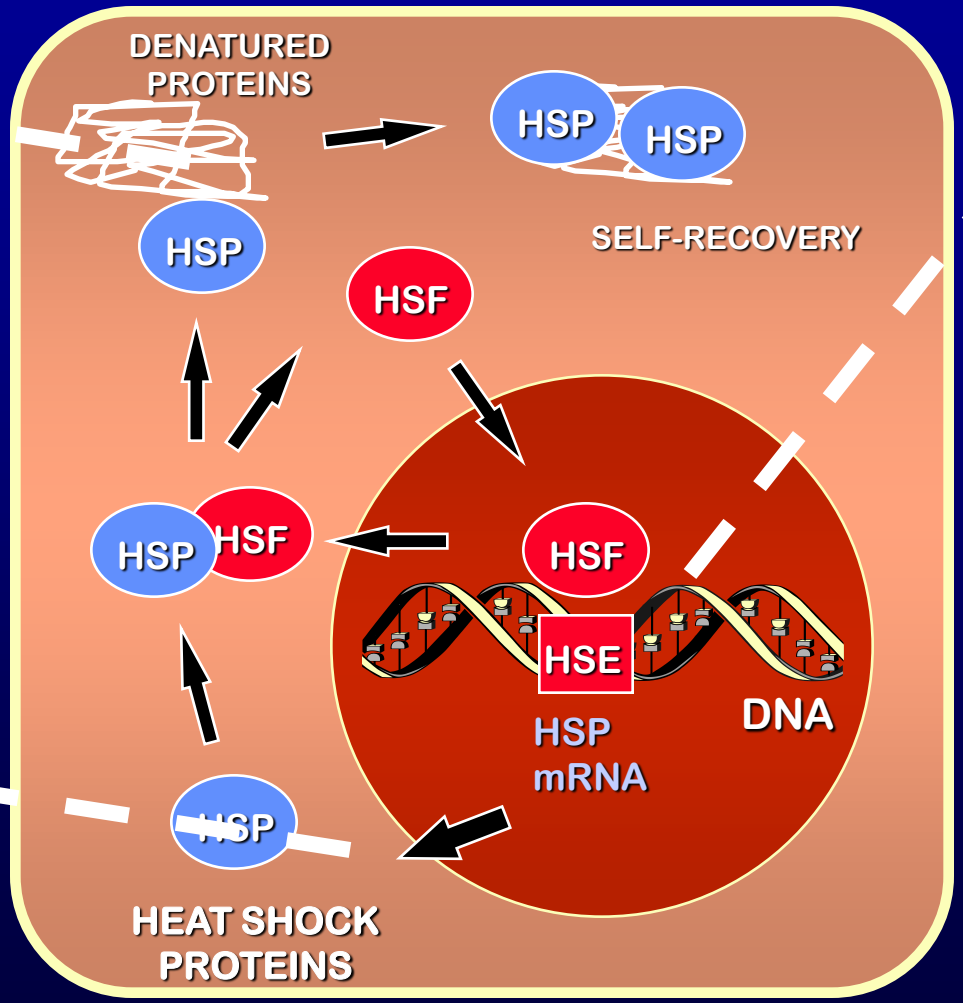
POSSIBLE MODELS EXPLAINING INVERSE EFFECTS (= SIMILIA PRINCIPLE) AT A CELLULAR LEVEL

- Detoxification enzymes (gene induction and activation)
- Heat shock proteins (stress proteins, chaperonins)
- Various receptors (different affinity and different coupling with effectors)
- Gating theory (signal transduction)

SUBOPTIMAL CELLULAR STRESS RESPONSE

EXCESS OF TOXIC LOAD

HORMONAL AND/OR METABOLIC IMBALANCE OF GENE EXPRESSION



SUBOPTIMAL PROTEIN SYNTHESIS

HEAT-SHOCK PROTEINS AND HOMEOPATHY

R. Van Wijk and F.A.C. Wiegant (1995-1998)

"Such a condition of the cell, in which the reaction to the threat is not optimal, may be considered pathological. The cell could then be considered a "sick system" with the damage insufficiently compensated"

"Here the question is whether compensation can be increased and whether the development of resistance can be stimulated, and if so, how"

HEAT-SHOCK PROTEINS AND HOMEOPATHY

R. Van Wijk and F.A.C. Wiegant (1995-1998)

"Self-recovery will be stimulated with a smaller dose of the substance responsible for disturbing the system in the first place"

"Self-recovery is defined on the cellular level as supplementing the arsenal of protective proteins, stimulating resistance for the disturbing agent and temporarily stimulating proliferation in compensation for cell death"

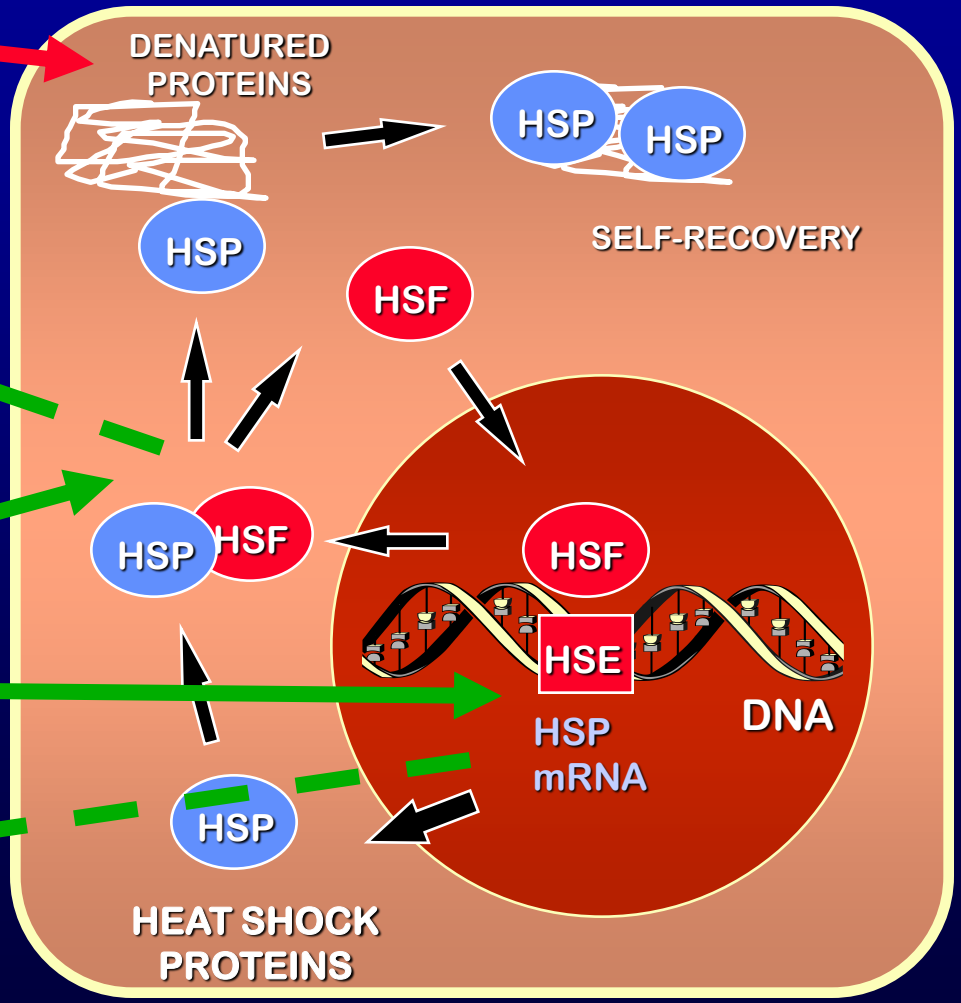
HYPOTHETICAL MODEL OF THE REGULATION OF CELLULAR STRESS RESPONSE BY LOW DOSES OF TOXIC COMPOUNDS

HIGH DOSES OF TOXIC COMPOUND

INCREASE OF FREE AND AVAILABLE HSP

LOW-DOSE "SIMILE" COMPOUND

INCREASE OF HSP mRNA TRANSCRIPTION



THERAPEUTIC APPLICATIONS OF HEAT SHOCK PROTEINS

S.M. Edginton Bio/TECHNOLOGY VOL. 13, DECEMBER 1995, p. 1442-1444

- Immune modulation
- Cancer therapy
- Vaccines and Adjuvants
- Heart attack and stroke

EXAMPLES OF INVERSE EFFECTS IN ANIMAL SYSTEMS

System	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

TREATMENT OF ORGAN-SPECIFIC AUTOIMMUNE DISEASES IN ANIMALS USING THE "SIMILE" SUBSTANCE

DISEASE	ADMINISTERED COMPOUND
Experimental allergic encephalomyelitis (Lewis rat, guinea pig)	Myelin basic protein Oral: 3-10 mg (no effect with 50 mg) Aerosol: 0.005-5 mg
Collagen-induced arthritis Adjuvant-induced arthritis BSA-induced arthritis (Lewis rat)	Collagen type II and type I Oral: 0.003 mg (no effect with 0.3 mg)
Spontaneous autoimmune diabetes (Mouse)	Insulin Oral: 1 mg (no effect with 5 mg)
Experimental autoimmune myastenia gravis (Lewis rat)	Acethylcholine receptor Oral: 20 mg

Adapted from Weiner et al., Annu. Rev. Immunol. 1994; 12: 809-837. The daily intake indicated

ANIMAL MODELS OF INVERSION OF EFFECTS (Verona group)

- Effects of high dilutions of histamin and other natural compounds on acute inflammation in rats

Conforti, A., Signorini, A. and Bellavite, P. (1993) In: Omeomed92 (C. Bornoroni ed.). Editrice Compositori, Bologna. pp 163-169.

- Intraperitoneal administration of adjuvant inhibits the development of adjuvant arthritis in rats

Conforti, A., Lussignoli, S., Bertani, S., Ortolani, R., Verlato, G. and Bellavite, P. (1995). Int. J. Immunopathol. Pharmacol. 8 (2): 113-121.

- Specific and long-lasting suppression of rat adjuvant arthritis by intraperitoneal low-dose of Mycobacterium butiricum.

Conforti A., Lussignoli, S., Bertani, S., Verlato, G., Ortolani, R., Bellavite, P. and Andrighetto, G. (1997) Eur. J. Pharmacol. 324: 241-247.

- Suppression of adjuvant arthritis in rats by intraperitoneal Mycobacterium butyricum

Conforti, A, Lussignoli, S., Bertani, S., Ortolani, R., Brendolan, A., Cestari, T., Andrighetto, G. and Bellavite, P. (1998). *J. Chemother.* 10: 169-172

- Dual effects of a homeopathic mineral complex on carrageenan-induced oedema in rats

Bertani, S., Lussignoli, S., Andrioli, G., Bellavite, P. and Conforti, A. (1999) *Br. Hom. J.* 88: 101-105

EXAMPLES OF INVERSE EFFECTS IN HUMANS

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
Cardiovascular 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
Nervous system	Tryciclic antidepressants	**Mood elevation in depressed patients**	**Sleepiness, low blood pressure, dysphoria**	Goodman 1990

Reviews: Bellavite/Signorini 1995; Eskinazi 1999

EXAMPLES OF MODERN SCIENTIFIC THERAPIES
IN AGREEMENT WITH THE PRINCIPLE OF SIMILARITY

- Cytokine therapy in the immunocompromised host
- Endotoxins as immunostimulants
- Treatment of immune disorders with immunoglobulins
- Nitric oxide in respiratory diseases
- Oral myelin in multiple sclerosis
- Oral collagen in rheumatoid arthritis
- Bacterial extracts in recurrent bronchitis
- Nasal allergens in allergic diseases
- Cancer vaccines made with tumour antigens or cells

SUMMARY OF EXPERIMENTAL EVIDENCE OF "SIMILIA PRINCIPLE"/INVERSION OF EFFECTS

- Stimulation or protection by low doses of toxic compounds (typical hormesis effect) on cell and animal models
- Inhibition of specific cellular activities by low doses of stimulating compounds
- Inhibition or protection of autoimmunity by low doses of antigen
- Paradoxical effects of drugs
- Therapeutic effects of low doses/high dilutions of toxic compounds in humans (classical homeopathy)