

Postconditioning Hormesis

Mild Stress Stimulates Recovery in Cells

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Overview

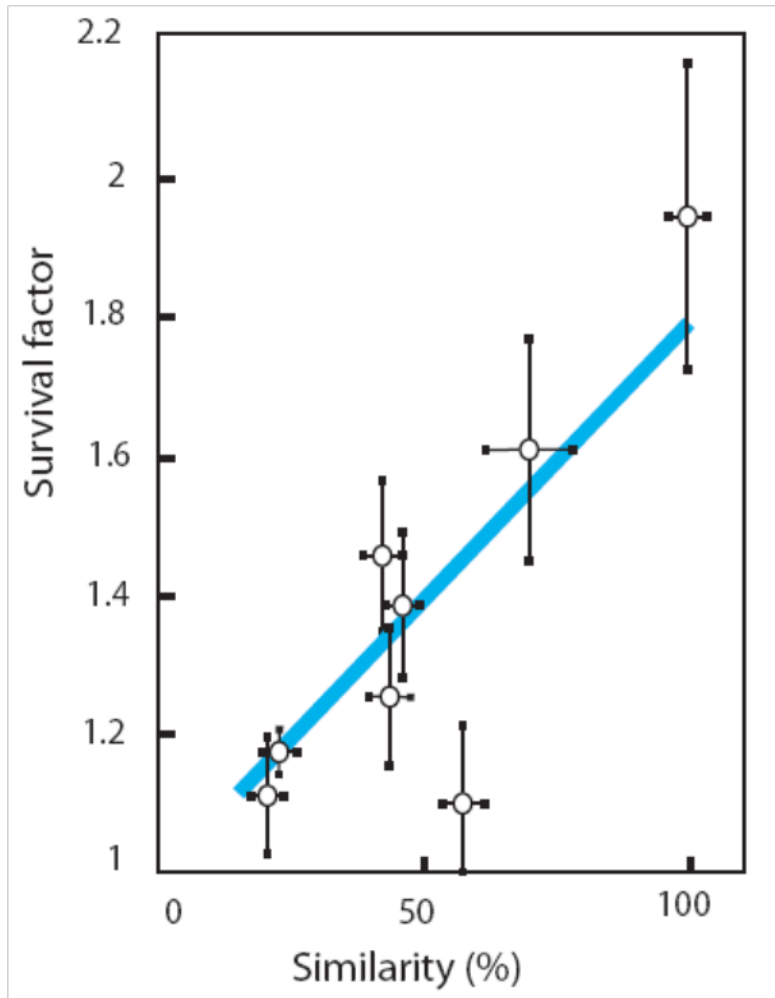
- ❑ Take-home message
- ❑ Definition of pre- and post-conditioning hormesis
- ❑ Cell studies
 - Examples of post-conditioning
 - Specificity of post-conditioning and the (homeopathic) Similia principle
- ❑ Clinical studies; some examples of post-conditioning
- ❑ Conclusion

Take home message

- ❑ Stress causes an imbalance in biological systems → stimulates (self)recovery → regaining homeostasis
- ❑ In post-conditioning, mild stress applied to already disturbed systems further supports (self)recovery
- ❑ Not all types of mild stress conditions are equally effective; there is specificity in the type of mild stress applied
- ❑ Effectiveness can be predicted using the Similia principle; the mild stress condition that shows the highest overlap with the more severe stress condition, with respect to the pattern of induced stress symptoms, is most effective.

Take home message (2)

□ Relation with the Similia principle?



The better the low dose stress resembles the high dose stress (in terms of induced 'symptoms'), the better (self)recovery is stimulated!!

**-Wiegant et al. Hum Exp Toxicol 1999;
18: 460-470**

Definition

- 'New' concept: 'post-conditioning' hormesis
 - The curative effect of low doses of stress
- Well-known concept: 'pre-conditioning' hormesis
 - The preventive effect of low doses of stress



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Toxicology
and Applied
Pharmacology

www.elsevier.com/locate/ytap

Short Communication

Biological stress response terminology: Integrating the concepts of adaptive response and preconditioning stress within a hormetic dose–response framework

Edward J. Calabrese^{a,*}, Kenneth A. Bachmann^b, A. John Bailer^c, P. Michael Bolger^d, Jonathan Borak^e, Lu Cai^f, Nina Cedergreen^g, M. George Cherian^h, Chuang C. Chiuehⁱ, Thomas W. Clarkson^j, Ralph R. Cook^k, David M. Diamond^l, David J. Doolittle^m, Michael A. Doratoⁿ, Stephen O. Duke^o, Ludwig Feinendegen^p, Donald E. Gardner^q, Ronald W. Hart^r, Kenneth L. Hastings^d, A. Wallace Hayes^s, George R. Hoffmann^t, John A. Ives^u, Zbigniew Jaworowski^v, Thomas E. Johnson^w, Wayne B. Jonas^u, Norbert E. Kaminski^x, John G. Keller^y, James E. Klaunig^z, Thomas B. Knudsen^{aa}, Walter J. Kozumbo^{ab}, Teresa Lettieri^{ac}, Shu-Zheng Liu^{ad}, Andre Maisseu^{ae}, Kenneth I. Maynard^{af}, Edward J. Masoro^{ag}, Roger O. McClellan^{ah}, Harihara M. Mehendale^{ai}, Carmel Mothersill^{aj}, David B. Newlin^{ak}, Herbert N. Nigg^{al}, Frederick W. Oehme^{am}, Robert F. Phalen^{an}, Martin A. Philbert^{ao}, Suresh I.S. Rattan^{ap}, Jim E. Riviere^{aq}, Joseph Rodricks^{ar}, Robert M. Sapolsky^{as}, Bobby R. Scott^{au}, Colin Seymour^{aj}, David A. Sinclair^{at}, Joan Smith-Sonneborn^{av}, Elizabeth T. Snow^{aw}, Linda Spear^{ax}, Donald E. Stevenson^{ay}, Yolene Thomas^{az}, Maurice Tubiana^{ba}, Gary M. Williams^{bb}, Mark P. Mattson^{bc}

Definition

- ❑ Beneficial effect of mild stress has been indicated as: ‘preconditioning’, ‘adaptive response’, ‘hormesis’, ‘autoprotection’, ‘Arndt-Schulz law’, ‘Yerkes-Dodson law’, etc.
- ❑ Consensus (Calabrese *et al.* 2007): ‘Hormesis’ as oldest term, already coined in 1943.
- ❑ Terminology
 - Hormesis
 - Pre-conditioning hormesis
 - Post-conditioning hormesis (only 1 example from clinical research?)

Definition

□ Post-conditioning hormesis

- Toxicity of high stressor dose is sometimes ameliorated by subsequent exposure to a low dose of the same stressor.
- One example mentioned by Calabrese et al. (2007)

Am J Physiol Heart Circ Physiol 285: H579–H588, 2003.
First published April 3, 2003; 10.1152/ajpheart.01069.2002.

Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning

Zhi-Qing Zhao, Joel S. Corvera, Michael E. Halkos, Faraz Kerendi,
Ning-Ping Wang, Robert A. Guyton, and Jakob Vinten-Johansen

Postconditioning hormesis

- Agutter (2008): More examples?
 - Any cell studies?,
 - Are there more experimental and clinical studies that show a stimulation of self-recovery by low dose stress?

American Journal of Pharmacology and Toxicology 3 (1): 97-107, 2008

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Elucidating the Mechanism(s) of Hormesis at the Cellular Level: The Universal Cell Response

Paul S. Agutter

Theoretical and Cell Biology Consultancy,
26 Castle Hill, Glossop, Derbyshire, SK13 7RR, UK

Postconditioning hormesis

- Wiegant, Prins and Van Wijk (2011): More examples!!
 - Cell studies,
 - Overview of experimental and clinical studies

Dose Response 2011; 9: 209-224

**POSTCONDITIONING HORMESIS PUT IN PERSPECTIVE:
AN OVERVIEW OF EXPERIMENTAL AND CLINICAL STUDIES**

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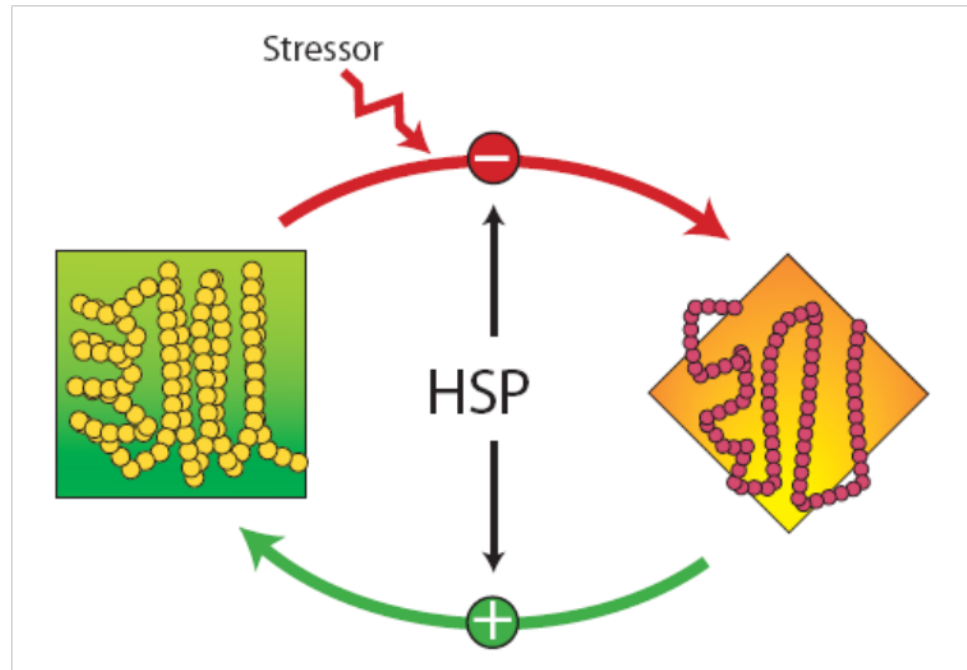
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The Netherlands; International Institute of Biophysics, Neuss, Germany

Postconditioning hormesis in cells

- Is low dose stress beneficial when applied to cell cultures that were previously stressed with a high dose of the same stress?
 - High dose arsenite → low dose arsenite
 - High dose cadmium → low dose cadmium
 - Heat shock → 'fever'

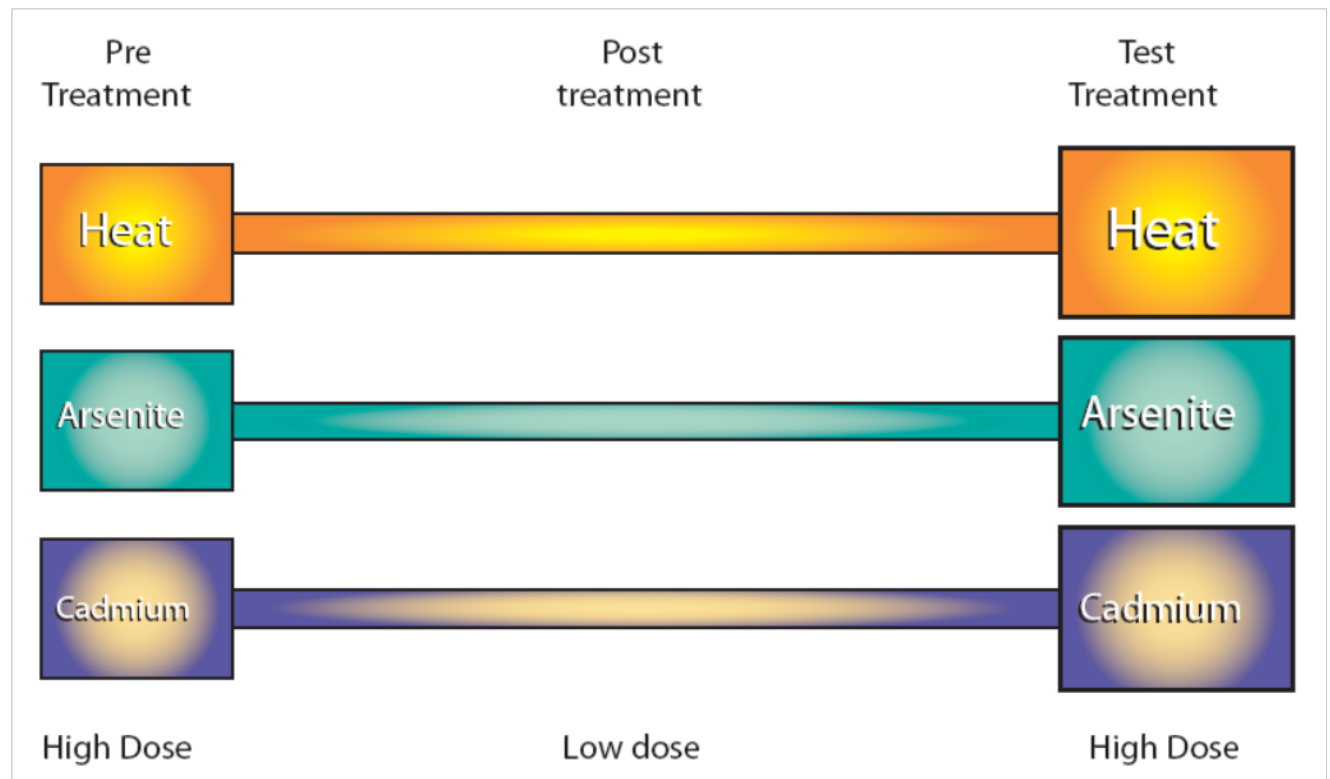
Postconditioning hormesis in cells

- Parameters? How to measure a possible beneficial effect in terms of (self-)recovery?
 - Synthesis of heat shock proteins (hsp)
 - Survival capacity (adaptive resistance against final test)



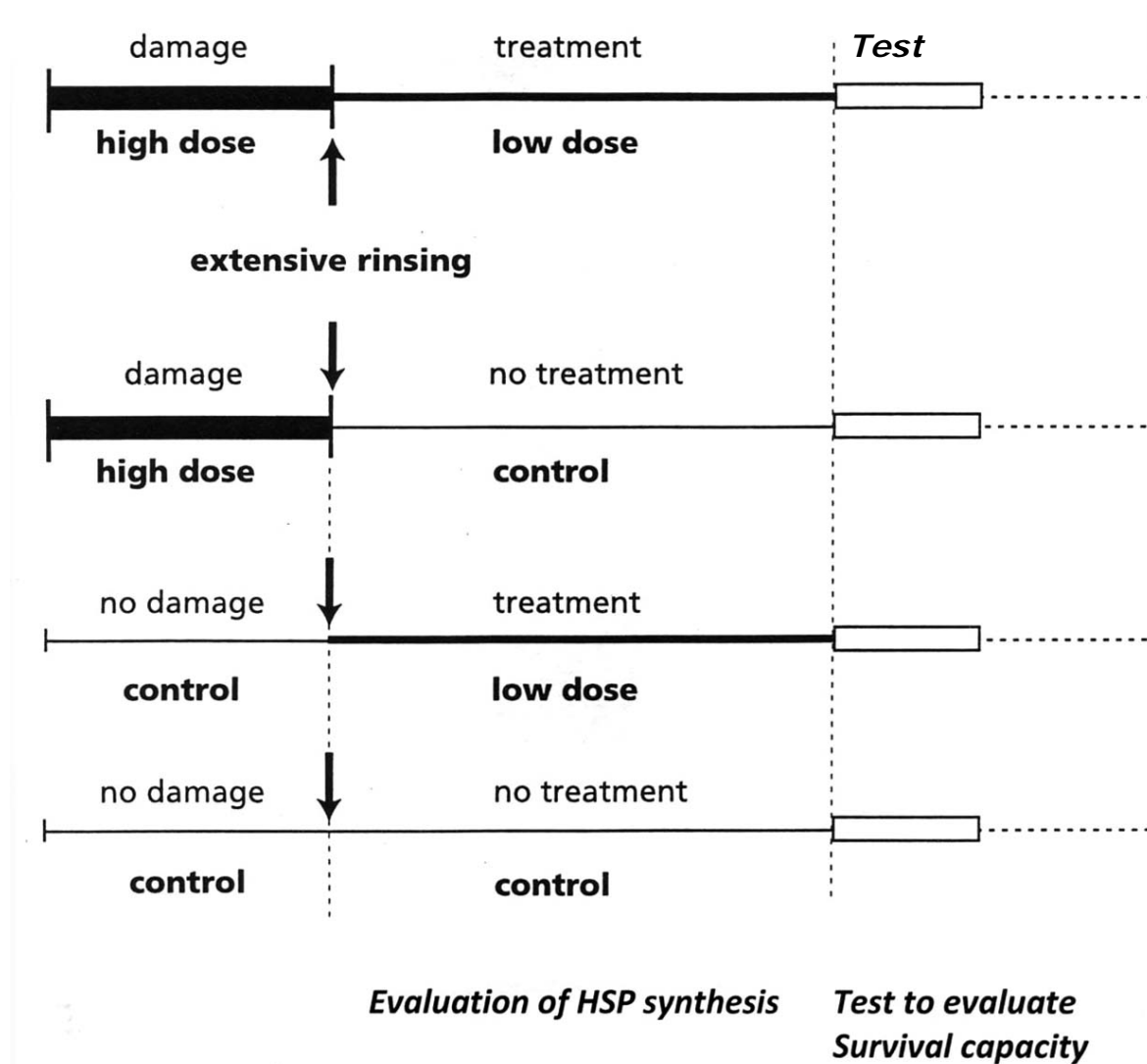
□ Main questions

- ## □ Protocol:



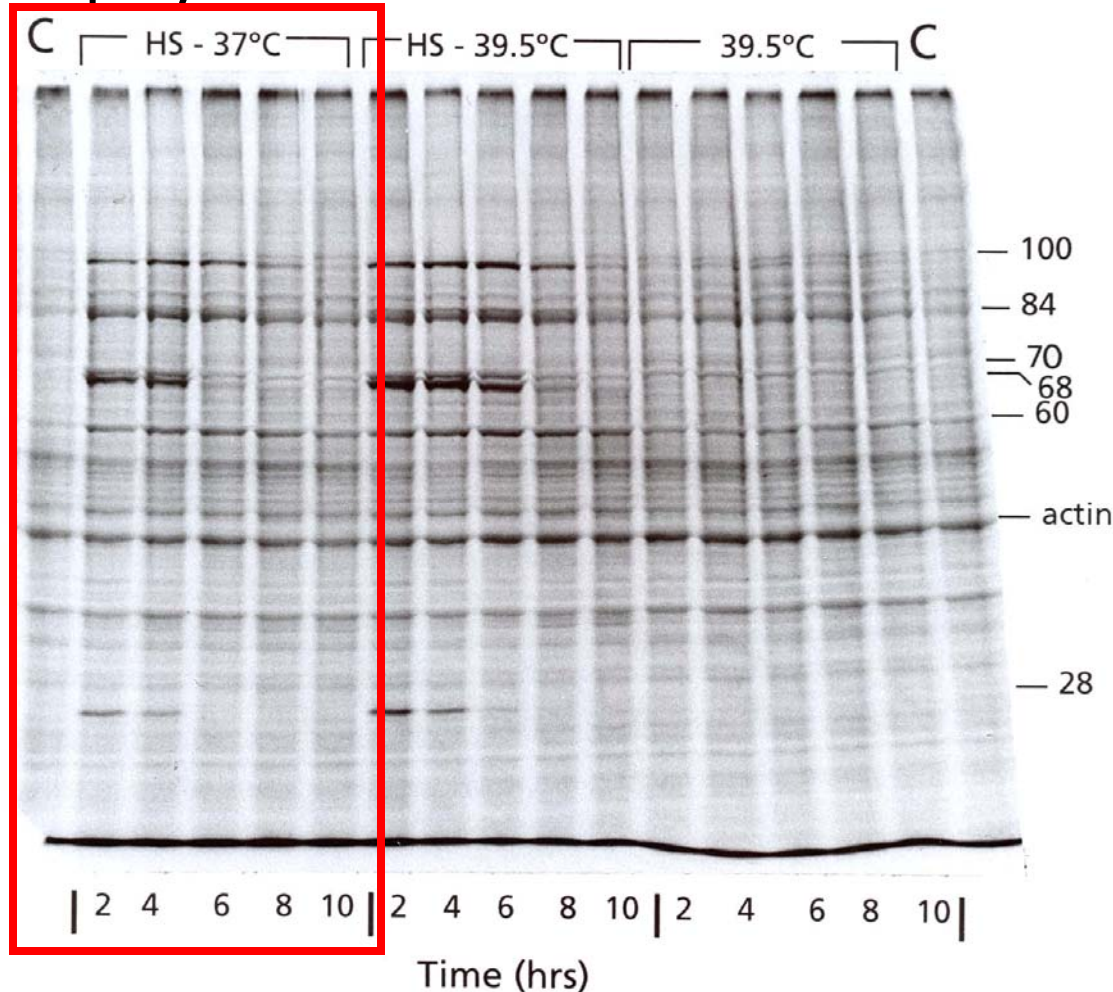
Postconditioning hormesis in cells

□ Protocol



Postconditioning hormesis in cells

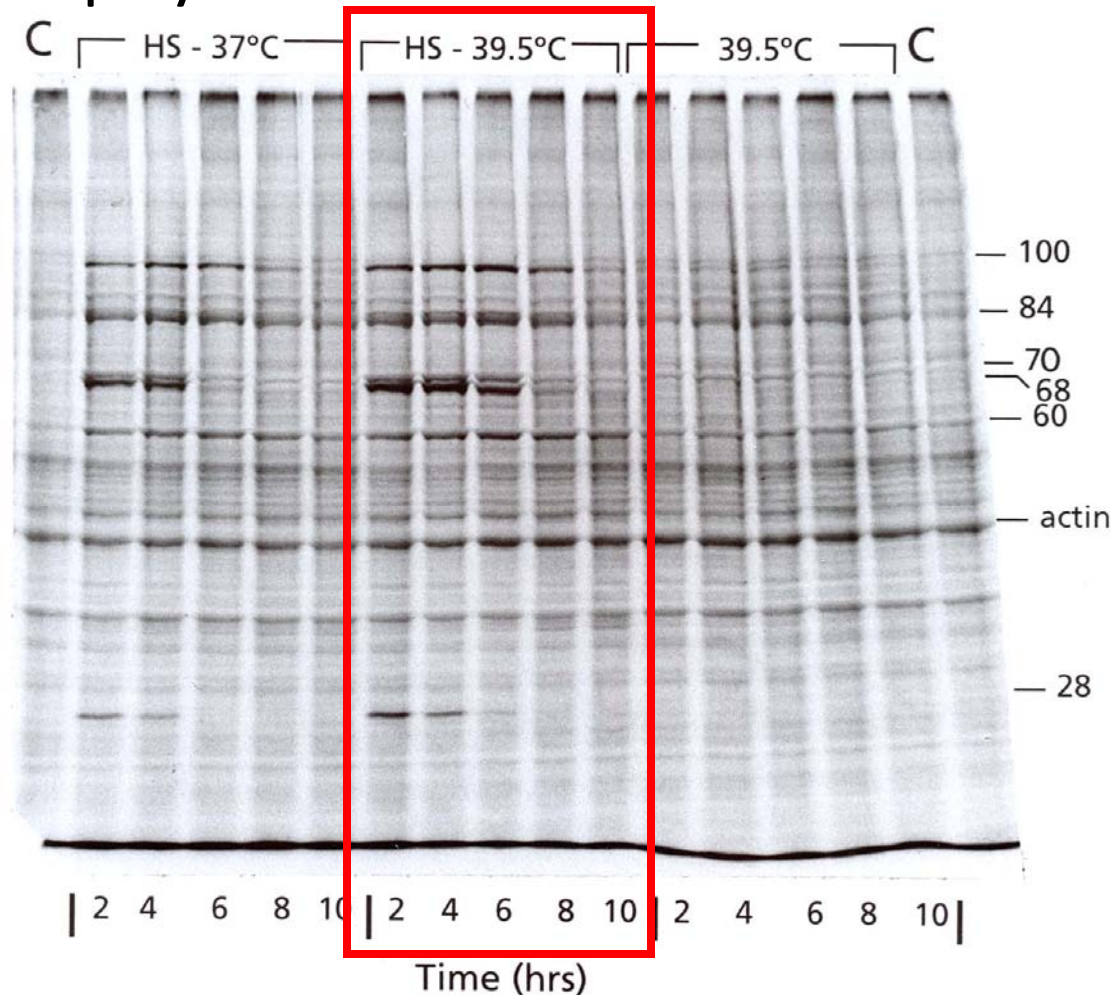
□ Hsp synthesis



- HS (30' 42°C) induces hsps
- HS-'fever': synthesis of hsps is enhanced & prolonged
- 'fever' itself is without effect

Postconditioning hormesis in cells

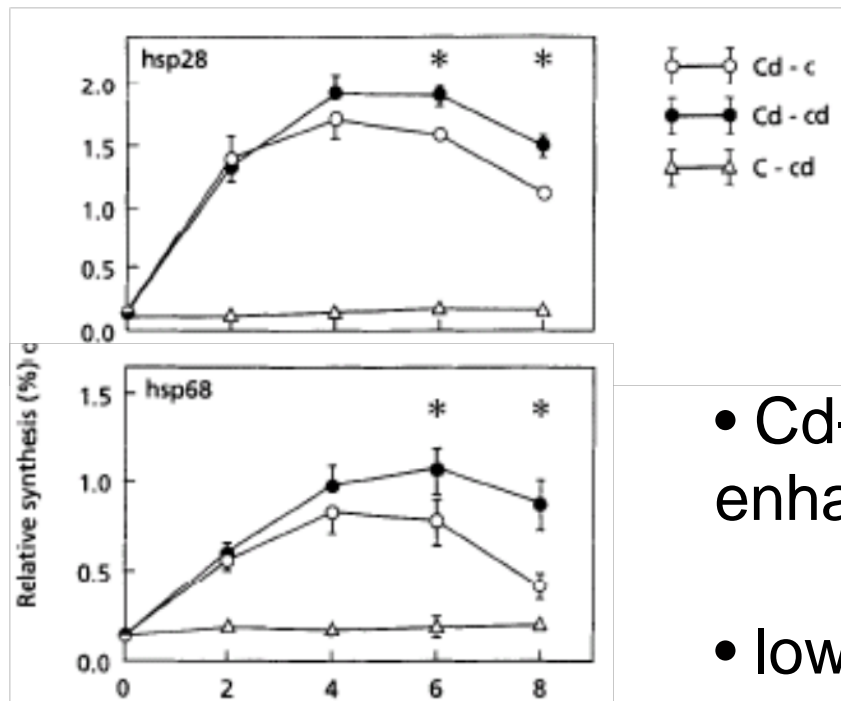
□ Hsp synthesis



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Postconditioning hormesis in cells

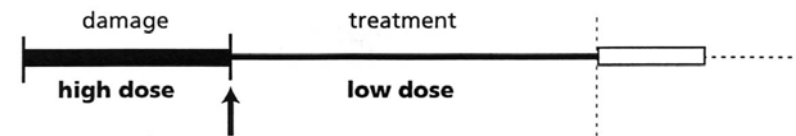
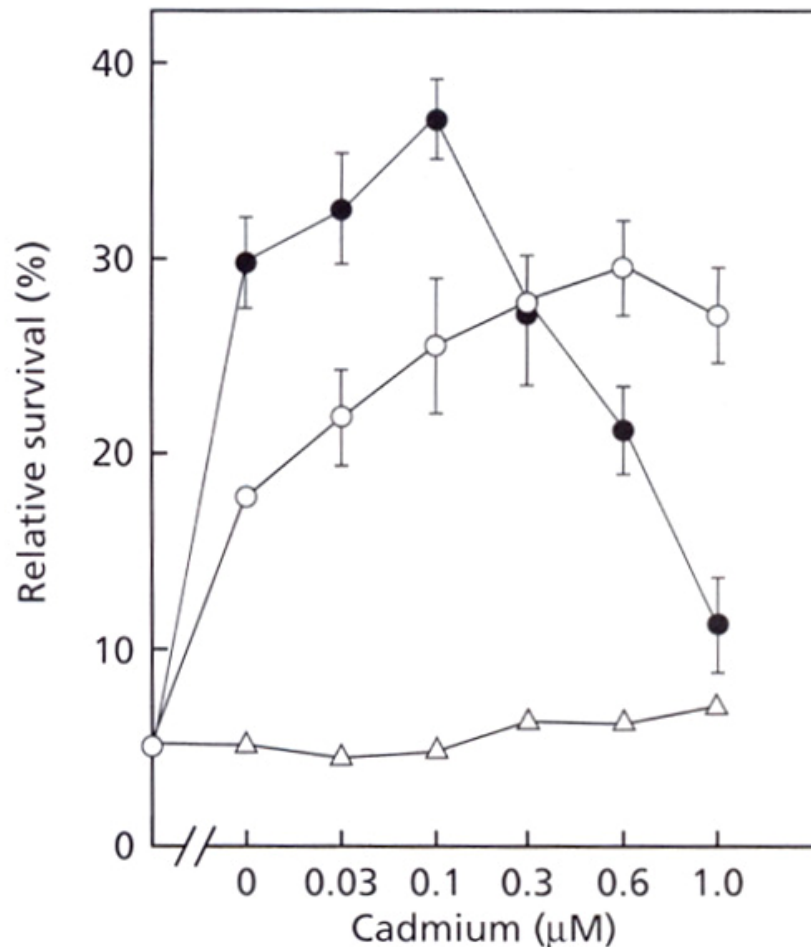
□ HSP synthesis: High dose Cd → low dose cd



- Cd-cd: synthesis of hsps is enhanced and prolonged
- low dose cd: itself is without effect on synthesis of hsps

Postconditioning hormesis in cells

□ Survival capacity: High dose Cd → low dose cd



Cd(10μM) – cd – Cd (50μM)
Cd(30μM) – cd – Cd (50μM)

- low dose cd: no effect
- Cd(10)–cd: increase in survival capacity due to low dose
- Cd(30)–cd: increase followed by decrease in survival capacity

Postconditioning hormesis in cells

- **Conclusions:** Low dose stress is able to:
 - enhance synthesis of hsps, and
 - enhance adaptive resistance (survival capacity)

- Effect of low dose stress depends on initial high dose damage:
 - large disturbance → low dose should be 'mild'
 - small disturbance → low dose can be 'stronger'

Postconditioning & similia

- What if the high dose stress is followed by a low dose of a different type of stress condition?
 - Are all stress conditions applied in low dose equally effective ?, Is there specificity?
 - Similia principle predicts specificity !

Postconditioning & similia

- Similia principle predicts that the low dose stress which induces a comparable pattern of symptoms as the high dose stress, will be most beneficial!
 - Similia principle is the therapeutic guideline in homeopathy: Symptoms of patient are matched with a remedy which is capable of inducing similar symptoms in healthy individuals
- Question: Is low dose stress most beneficial if there is a similarity with 'symptoms' induced by the high dose?

Postconditioning & similia

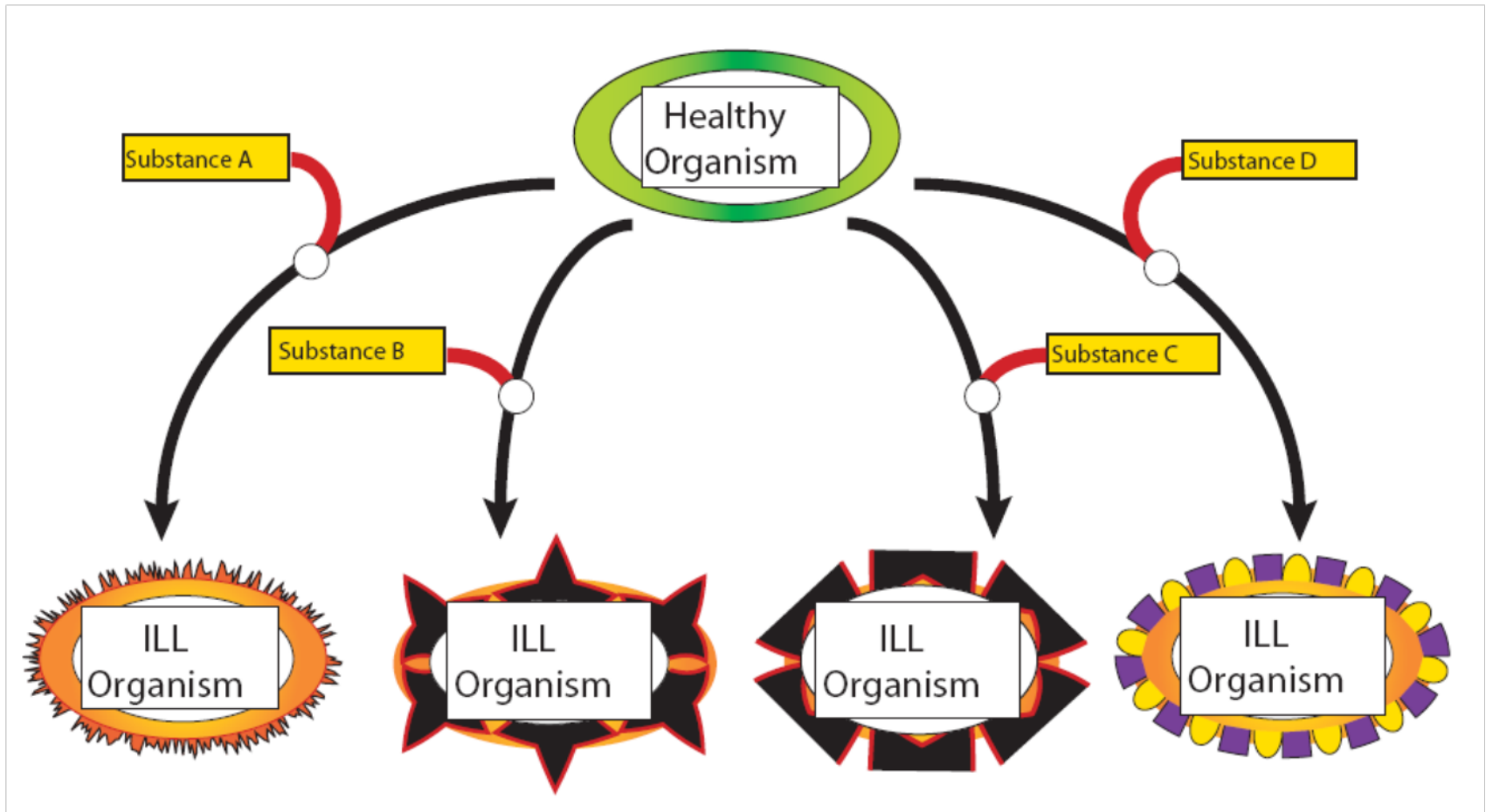
□ Protocol:

1. Determine the 'symptom pattern' of stress conditions at the cellular level
2. Expose cells to a high stress condition
3. Apply different stress conditions in low dose
4. Evaluate stimulation of recovery

□ Hypothesis: Low dose of stress condition which most resembles the pattern of symptoms induced by the high stress dose, will stimulate recovery most effectively!

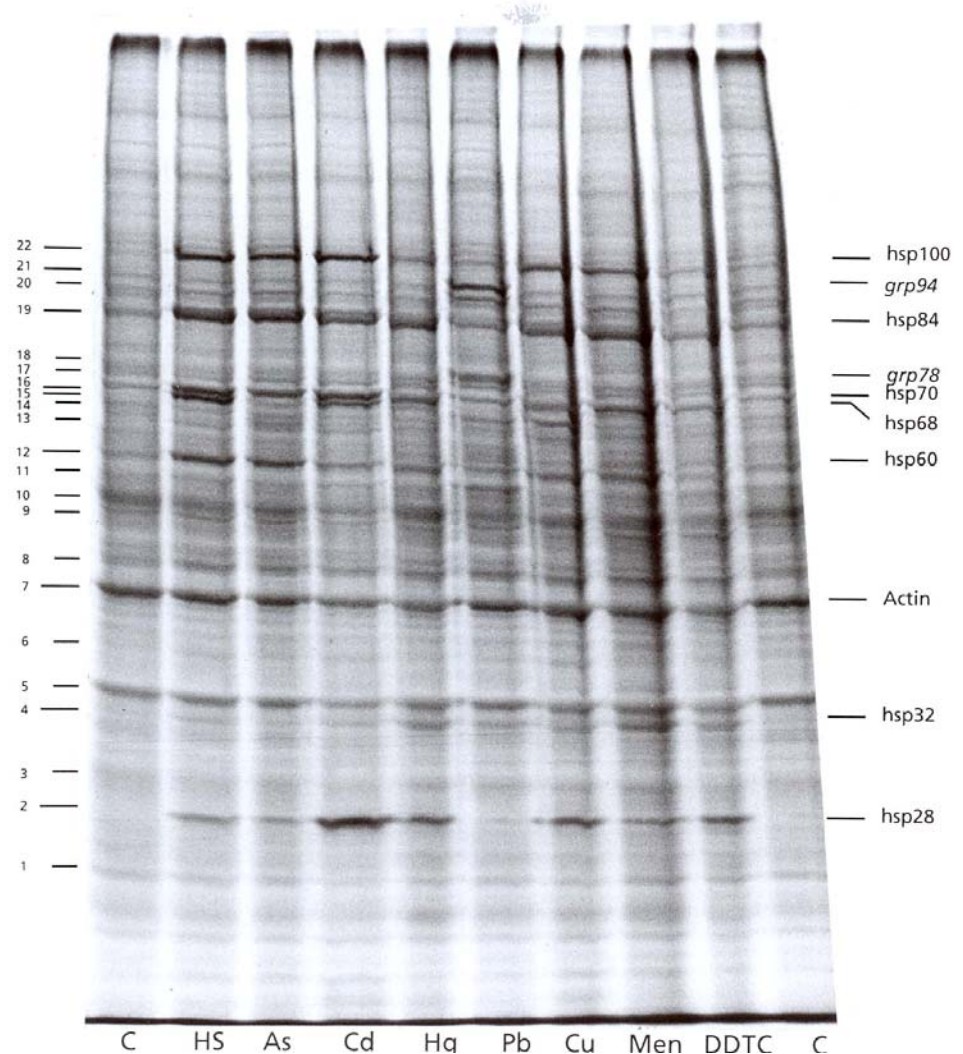
Similia & Postconditioning

□ Symptom pattern ('remedy picture')



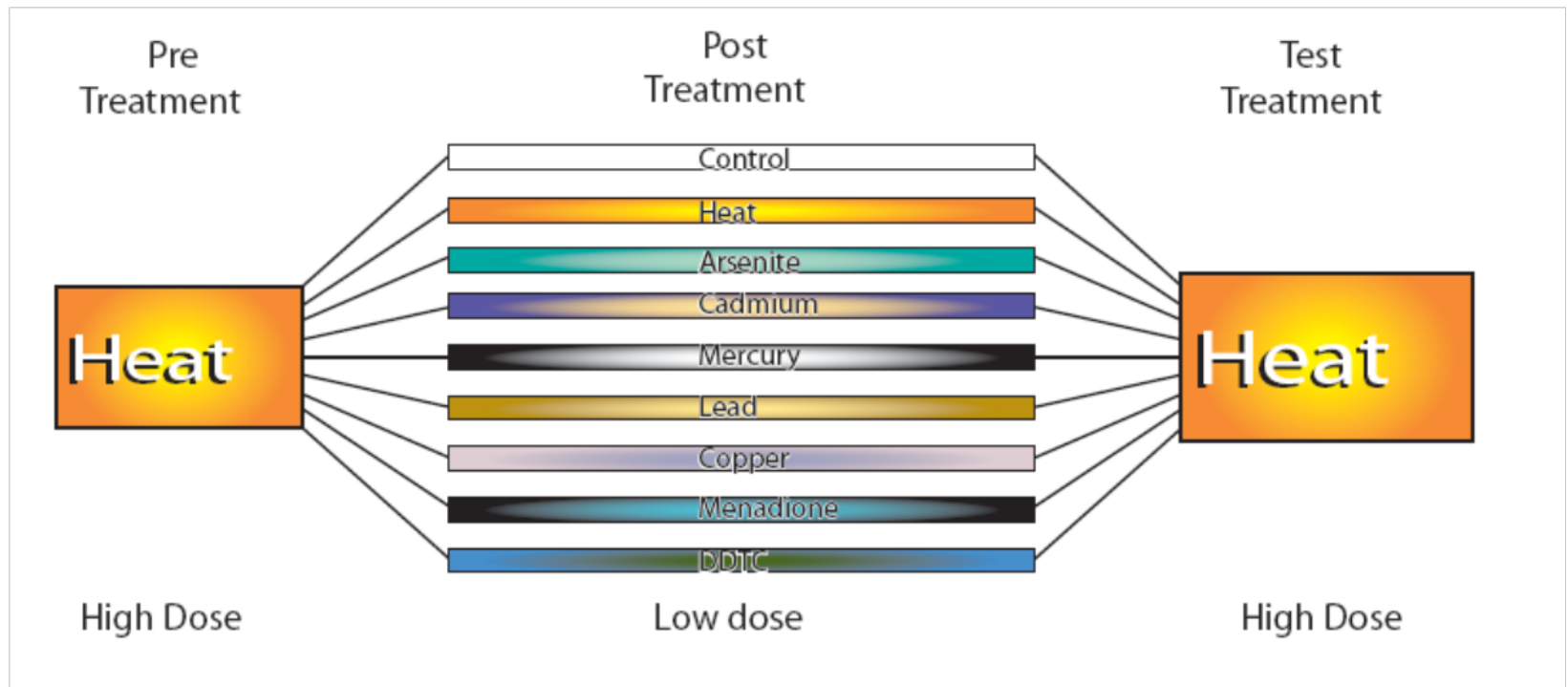
Similia & Postconditioning

- Symptom pattern / 'remedy picture'
- Similarity between stress conditions is determined based on hsp-'symptoms'
- Similarity can be quantified.



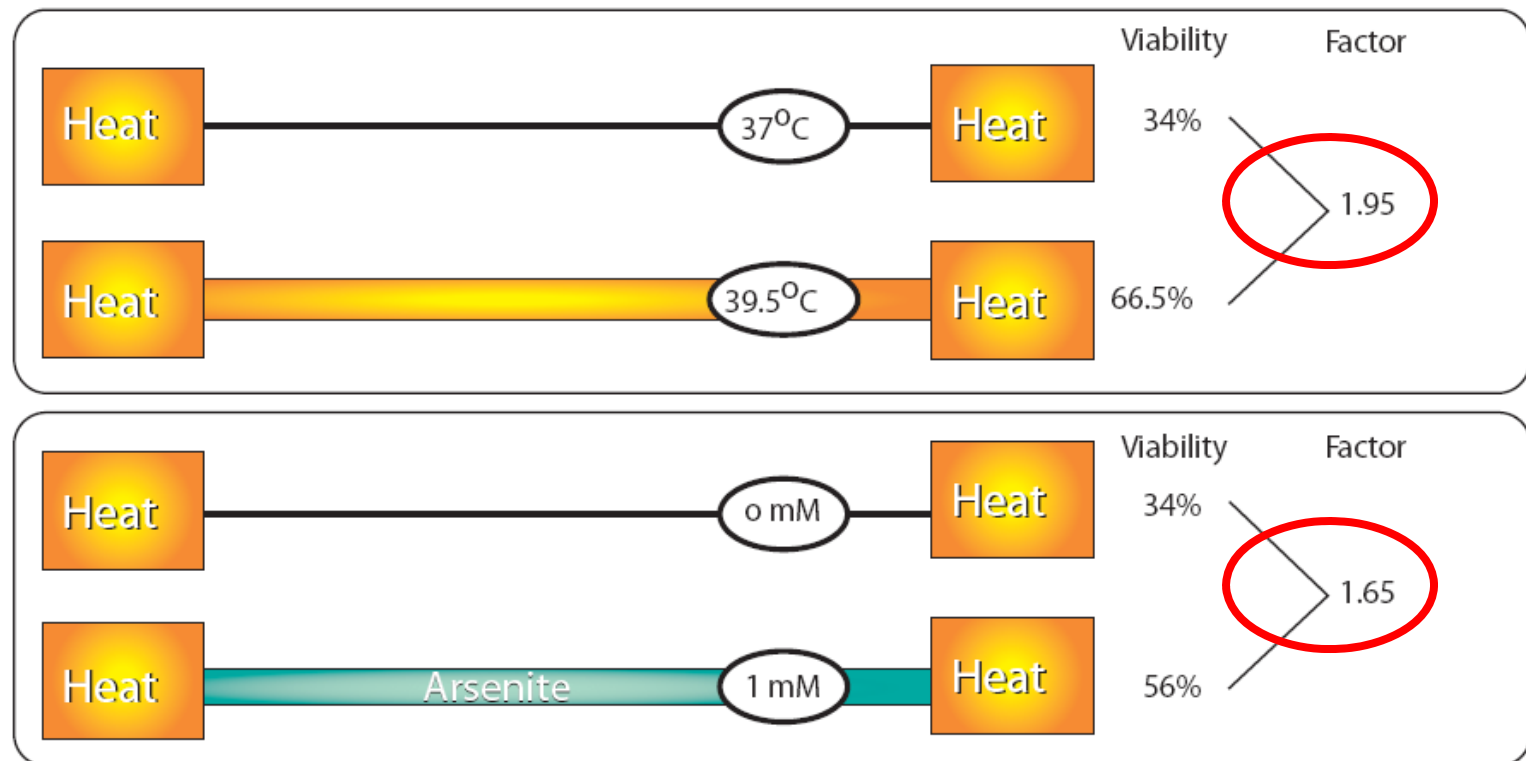
Similia & Postconditioning

- High dose stress is followed by incubation in different low dose stress conditions. Finally, they are exposed to a test treatment (to evaluate survival capacity)



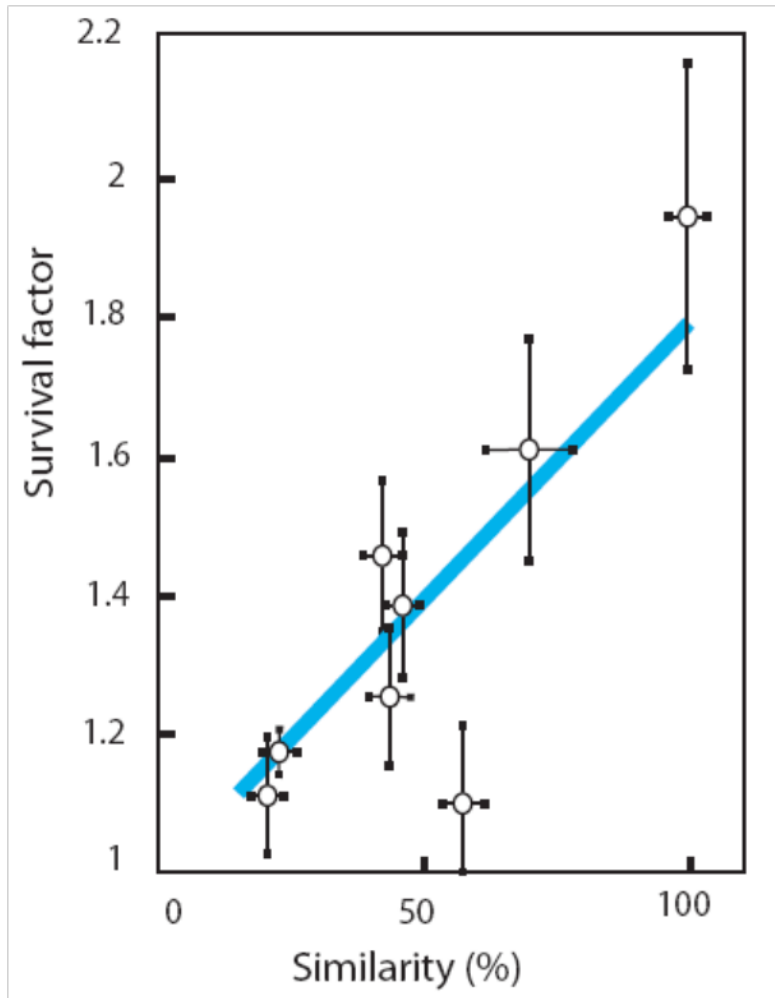
Similia & Postconditioning

- **Hypothesis:** When symptom pattern of high dose- & low dose stress condition resembles each other most, stimulation of recovery will be most effective!



Similia & Postconditioning

□ Relation with the Similia principle?



The better the low dose stress resembles the high dose stress (in terms of induced 'symptoms'), the better (self)recovery is stimulated!!

- Wiegant et al. Hum Exp Toxicol 1999;
- Wiegant & van Wijk. Homeopathy 2010; 99: 3-14

Experimental & Clinical studies

- Examples of postconditioning hormesis
 - Immunology
 - Cardiovascular
 - Brain ischemia
 - Fobia's, psychological disorders

For further details on examples:

Wiegant FAC, HAB Prins and R van Wijk. 'Postconditioning put in perspective; an overview of experimental and clinical studies'. Dose Response 2011; 9: 209-224.

Conclusions: postconditioning hormesis

- Beneficial effect of low dose stress in cell studies:
 - Low dose stress applied post-conditionally supports recovery: enhanced synthesis of hsp's and further increase in survival capacity
 - Relationship between high dose-low dose; low dose can also be detrimental (in case pre-stress was severe)
 - There is specificity in the low dose effect

- There are many examples of experimental and clinical studies of 'Post-exposure conditioning hormesis'

Thanks for your attention!



Any questions?

References

- ❑ Agutter
- ❑ Calabrese et al. *Toxicol Appl Pharmacol*. 2007; 222: 122-128
- ❑ Wiegant FAC, Wiegant FAC, Souren JEM and Van Wijk R. 1999. Stimulation of survival capacity in heat-shocked cells by subsequent exposure to minute amounts of chemical stressors: Role of similarity in hsp inducing effects. *Hum Exp Toxicol*. 1999; 18: 460-470.
- ❑ Wiegant FAC, Prins HAB, van Wijk R. Postconditioning hormesis put in perspective; an overview of experimental and clinical studies. *Dose Response*. 2011; 9: 209-224.