

Cultured
mammalian cells
the similia principle
in *in self-recovery*
homeopathy
research

**Cultured mammalian cells in homeopathy
research**

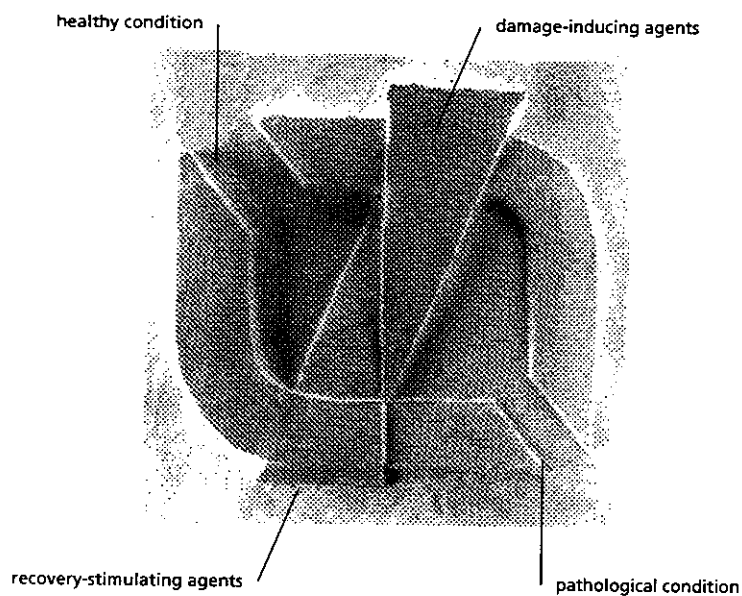
The similia principle in self-recovery

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An artist impression* of the basic principles of homeopathy

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Preface

In this report an account is given of cell - and molecular biological research into the similia principle in cultivated isolated animal cells. The pattern of molecular changes playing a role in the recovery of cells after an exposure to a threatening condition were investigated and the possibility of stimulating this recovery by the application of the similia principle.

The research was carried out at the Department of Molecular Cell Biology within its research program "Differentiation and gene expression". In the period 1990 - 1994, the study was financed by Homeopathy International, which is represented in The Netherlands by VSM Geneesmiddelen BV.

The research scientists are Dr. R. van Wijk (project coordinator), Dr. F.A.C. Wiegant, Dr. J.E.M. Souren and Drs. J.H. Ovelgönne.

The study of the hsp70 autoregulation has taken place within a cooperation project with the Department of Medical Physics and Informatics of the University of Amsterdam. We would like to thank Dr. A. Peper and Prof. Dr. Ir. C.A. Grimbergen, who developed the mathematical model of the hsp70 regulation cycle.

The study on the development of tolerance has taken place within a cooperation project with Dr. J. van Rijn at the Department of Radiotherapy of the Free University of Amsterdam.

We thank J.M. van Aken, J. van den Berg, A.W.J.M. Bol, Dr E. Boon-Niermeyer, Dr. M.J.M. Tuijl, Dr. C.A. Van der Mast and Prof. Dr. H.O. Voorma for their specific contribution to the realization of the study and the final report. Finally we would also like to thank the various students who have contributed to the execution of the many experiments as part of their research training in the biomedical

education: Harmke Ooms, Miranda Annink, Stefan Hogervorst, Stephan Alink, Machteld van Schoot, Karen Jaarsveld, Esther de Koning, Marij Welters, Bellinda Bladergroen, Anne Hollinga, Gerben Koning, Brigit Heemskerk, Maaïke Kockx, Nienke van Hove, Ellen Dahler, Sanne van Delft, Ieke Roozendaal, Maikel Bitorina, Jeroen Maertzdorf, Bianca Brundel, Nicole Spieker, Michael Gesser and David van Brummelen.

In this report an overview is given of the outcome of the research. These results will be published in more detail elsewhere. Some publications already appeared in the international biomedical journals, while others are in preparation. A list of these articles and manuscripts in preparation on which the various chapters are based is given in appendix A.

Throughout the report a smaller lettertype has been used to give either background information or a description of methods. *Italics* are used to highlight statements, summaries or concluding remarks.

We hope that this approach to self-recovery processes at the cellular level and the stimulation of these processes will contribute to the discussion about the fundamental basis of the homeopathic treatment and will constitute a point of departure for the contact between the research of homeopathic principles and biomedical scientific research.

Utrecht, November 1994

Intro

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List of publications of the project

1. Introduction

Ooms H., Bol A.W.J.M., van Meer J.H. and Van Wijk R. (1993). Hormesis, een knelpunt in dosis-effect relaties. *Pharmaceutisch Weekblad* 128: 1118-1122.

Van Wijk R., Ooms H., Wiegant F.A.C., Souren J.E.M., Ovelgönne J.H., van Aken J.M. and Bol A.W.J.M. (1994). A molecular basis for understanding the benefits from subharmful doses of toxicants; an experimental approach to the concept of hormesis and the homeopathic similia law. *Environmental Management and Health* 5: 13-25.

2. Cellular aspects of self-recovery

Van Wijk R., Otto A.M. and Jimenez de Asua L. (1984). Effect of serum and growth factors on heat sensitivity in Swiss mouse 3T3 cells. *Journal of Cellular Physiology* 119: 155-162.

Van Wijk R., Otto A.M. and Jimenez de Asua L. (1984). Hyperthermia can enhance the initiation of DNA synthesis stimulated by growth factors in Swiss mouse 3T3 fibroblasts. *Experimental Cell Research* 153: 522-527.

Van Wijk R., Otto A.M. and Jimenez de Asua L. (1985). Increase of epidermal growth factor-stimulated cell-cycle progression and induction of thermotolerance by heat shock: temperature and time relationship. *International Journal of Hyperthermia* 1: 147-156.

3. The molecular basis of growth stimulation after damage

Tuijl M.J.M., Den Boon J.A., Van Grunsven W.M.J. and Van Wijk

R. (1991). Responsiveness of the increase in c-fos mRNA levels depends on the inducer and the cell's past. *Journal of Cellular Physiology* 149: 44-49.

Van Wijk, R., Welters, M. Souren, J.E.M., Ovelgönne J.H. and Wiegant, F.A.C. (1993). Serum-stimulated cell cycle progression and stress protein synthesis in C3H10T1/2 fibroblasts treated with sodium arsenite. *Journal of Cellular Physiology* 155: 265-272.

Van Delft S., Coffey P., Kruijer W. and Van Wijk R. (1993). C-fos induction by stress can be mediated by the SRE. *Biochemical and Biophysical Research Communications* 197: 542-548.

4. The molecular basis of heat shock and arsenite stimulated tolerance

Tuijl M.J.M., Cluistra S., Van der Kruijssen and Van Wijk R. (1993). Heat-induced unresponsiveness of heat shock gene expression is regulated at the transcriptional level. *International Journal of Hyperthermia* 9: 125-136.

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Souren J.E.M., Wiegant F.A.C. and Van Wijk R. Comparative study on the responsiveness to heat shock, arsenite, cadmium and ischemia of fibroblasts, neuroblastomas, hepatomas and myocytes: studies on tolerance and heat shock protein synthesis. Manuscript in preparation/ In experimentation phase.

5. The relationship of the heat shock-induced hsp70 synthesis to the thermal denaturation of cell protein

Van Wijk R., Van Aken J.M. and Schamhart D.H.J. (1993). Temperature-dependency of the expression of heat shock proteins in rat hepatoma cells with a different degree of heat sensitivity. *International Journal of Hyperthermia* 9: 137-150.

Souren J.E.M., Van Miltenburg C. and Van Wijk R. Relationship of the heat shock-induced hsp70 synthesis and the thermal denaturation of cell protein of Reuber H35 cells.

Manuscript in preparation/ In experimentation phase.

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Van Wijk R., Ovelgönne J.H. and Van Aken J.H. Relation between HSP68-mRNA levels and the rate of protein synthesis. Manuscript in preparation.

Van Rijn J., Van den Berg J., Souren J.E.M., Van Wijk R., and Joenje H. Heat shock protein synthesis in hepatoma cells continuously proliferating under normally lethal hypethemic stress and during decay of thermoresistance at 37°C. *International Journal of Hyperthermia*, in revision.

Ovelgönne J.H. and Van Wijk R. Modulation of hsp68 gene expression after heat shock in thermosensitized and thermotolerant cells is not solely regulated by binding of HSF to HSE. *International Journal of Hyperthermia*, in revision.

6. Towards a mathematical model of the regulation of hsp70 levels

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Wiegant F.A.C., Souren J.E.M., Van Rijn J. and Van Wijk R. (1993). Arsenite-induced sensitization and self-tolerance of Reuber H35 hepatoma cells. *Cell Biology and Toxicology* 9: 49-59.

Ovelgönne J.H., Souren J.E.M., Wiegant F.A.C. and Van Wijk, R.
Relationship between cadmium induced expression of heat shock
genes, inhibition of protein synthesis and cell death.
Toxicology (in revision).

8. The stimulation of self-recovery by application of the similia- principle

Schamhart D.H.J., Zoutewelle G., van Aken J.M. and Van Wijk R.
(1992). Effects on the expression of heat shock proteins by
step-down heating and hypothermia in rat hepatoma cells with a
different degree of heat sensitivity. *International Journal of
Hyperthermia* 8: 701-716.

Van Wijk R., Ovelgönne J.H., de Koning E., Jaarsveld K., Van Rijn
J. and Wiegant F.A.C. (1994). Mild step-down heating causes
increased transcription levels of hsp68 and hsp84 mRNA and
enhances thermotolerance development in Reuber H35 hepatoma
cells. *International Journal of Hyperthermia* 10: 115-125.

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Wiegant F.A.C. Enhancement of the stress response by low
concentrations of arsenite in arsenite-pretreated H35 hepatoma
cells. *Toxicology and Applied Pharmacology* (in revision)

9. The specificity of the similia-principle

Wiegant F.A.C., Souren J.E.M., Van Rijn J. and Van Wijk R. (1994).
Stressor-specific induction of heat shock proteins in rat hepatoma
cells. *Toxicology* (in press)

Ovelgönne J.H., and Van Wijk R. Stressor-specific increase in levels
of the hsp60 mRNA, hsp68 mRNA and hsp84 mRNA and stressor-
unspecific activation of HSF in Reuber H35 hepatoma cells.
Manuscript in preparation.

Wiegant F.A.C., Souren J.E.M. and Van Wijk R. Stressor-induced
unresponsiveness of stress gene expression is for the same stressor
only. Manuscript in preparation

Wiegant F.A.C., Souren J.E.M. and Van Wijk R. Specificity in the
enhancement of the stress response by low concentrations of
stressors in stressor-pretreated H35 hepatoma cells.
Manuscript in preparation.