

“IS HORMESIS APPLICABLE AS A PRO-HEALTHY AGING INTERVENTION IN MAMMALS AND HUMAN BEINGS, AND HOW?”

INTRODUCTION TO A SPECIAL ISSUE OF *DOSE-RESPONSE*

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The effects of a mild stress on aging are no longer *terra incognita*, because in the last two decades several teams have published positive and promising results on the matter (reviews in Le Bourg and Rattan 2008). This is a far cry from the statement by Sacher (1977) that “hormesis is in one sense an obstacle in the path of gerontological research”, because hormetic effects “are unlikely to occur in the healthy active individual, and are more likely to be significant in the ill or depressed animal”. We have now gathered various experimental results, mainly in invertebrates, showing favorable effects of mild stress on aging and also a few clinical ones, but only a very few experimental studies have been done in mammals. Results on human beings are promising and motivate a debate among experts (the present issue) on the use of mild stress as a clinical tool or in prevention of some effects of human aging. The purpose of this introduction is not to summarize the articles of these invited experts but, rather, to draw attention on some points of interest.

In 2006, the guest editors of the present issue arranged a debate in *Biogerontology* (Vol.7, issue 3) to know whether experts were thinking that dietary restriction could increase longevity in all species, and particularly in human beings. To our surprise, one half of the authors answered “Yes” and the second half “No” (if we except an article concluding “Can’t know”). We were therefore expecting that some authors would argue in the present issue that mild stress could improve aging in experimental animals, but definitely would not in human beings. It was not the case. Obviously, all invited authors know that mild stress is efficient in human beings in some occasions, e.g. in cardiology (see the article by Abete *et al.* 2010), and we did not expect that they would argue that these results can

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be discarded. Nevertheless, beyond these results in cardiology, no author has argued that it is impossible to rely on hormesis to improve healthspan in human beings. Therefore, all authors have provided the same answer to the question “Is hormesis applicable as a pro-healthy aging intervention in mammals and human beings?” and this answer is “Yes”.

Most authors consider that answering to the second part of the question (“and how?”) will not be an easy thing. The devil is in the details, because using a mild stress in human beings is a source of many ethical and practical questions. Most articles in the present issue have emphasized that a stress can be “mild” (favorable effects?) for a given individual or “strong” (deleterious effects) for another one (see e.g. Rattan and Demirovic 2010). In addition, a stress can be a mild one at one age and a strong one later in life and we probably cannot perform the experiment to know whether it were strong, for obvious ethical reasons. A mild stress could also become a strong one if used in people already subjected to another stress (see Sørensen *et al.* 2010). The basic questions are thus: what mild stress could be used, when, with what dose?

Answering to the first question seems to be rather easy: exercise is probably the best candidate (see e.g., Marques *et al.* 2010, Pardon 2010), but heat stress is another one (e.g., Le Bourg 2010, Vaiserman 2010). It has also been argued that chemicals (see Hayes 2010) could be a nutritional stimulus with favorable effects. Yet, this is a short list of stresses and the imagination of scientists is strongly required to discover new mild stresses in human beings.

Answering to “When” using a mild stress will make sense probably after a mild stress had been selected. Anyway, we should already try to answer to the following question: should we apply the mild stress at a young age, as in experimental models, or only at old age? It will be probably hard to convince young people to engage in a “mild stress” therapy in the hope to improve their life when old. Elderly people would probably be more easily convinced, but would a mild stress still be efficient at this age (Abete *et al.* 2010)?

Finally, the question “What dose?” is dependent on the answer to the previous questions. Unfortunately, we will probably have to answer all these questions at the same moment. Taking into account all these problems, Kahn and Olsen (2010) stress that “it is more likely that hormetic therapy will become popular as treatment when used as an adjunct to other treatment strategies for serious illnesses”, rather than in “normal healthy individuals”. The other authors may probably consider this view as a little pessimistic one.

Therefore, the road towards using mild stress in human beings is probably more like a dirt track with many ruts than like a highway. It is the hope of the guest editors that the present debate among experts will provoke new studies on the use of hormesis in human beings.

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