



How hormesis and the potential health benefits of repeated mild stress of choice might change the way we age

In this exclusive interview, Gisèle Wertheim Aymés spoke with Professor Suresh Rattan, a scientist based at the Department of Molecular Biology and Genetics at Aarhus University in Denmark, and a speaker at IAGG (International Association of Gerontology and Geriatrics) 2013, in Seoul, South Korea.



BIOLOGICAL SYSTEMS AS DYNAMIC ENTITIES

Homeodynamics, which is essentially “the means by which we live and exist”, has led Rattan to formulate the concept of a “homeodynamic space” as the survival ability or buffering capacity of living systems, which can be the basis of understanding health, aging and longevity.

He explains: “From the classical textbooks we all know about homeostasis. Homeostasis applies only when the body is considered as a static and stable machine that exists in the same state all the time. It is a mechanical concept. In the last 20 years, we have realised that a biological system is actually a dynamic entity. It exists not by being in the same state, but by the same dynamics with which biological systems respond, adapt and survive. Changes keep happening in the biological systems that appear to keep the system apparently static. There is not a single cell in an organism that is static. Not even a single biomolecule! From the molecular level upwards, biological systems are constantly dynamic and not the same in the next unit of time.”

He says age-related health problems for which there are no clear-cut causative agents, except the complex process of aging, may be better tackled by focusing on health mechanisms and their maintenance, rather than disease management and treatment.

“Disease-oriented research approaches are economically, socially and psychologically unsustainable as compared with health-oriented and preventive strategies, such as hormesis.”

He explains this by using the example of an apparently healthy child who is born with a certain extent of homeodynamic space and a lot of survival mechanisms, but with a significant zone of vulnerability. “That is why a lot of things can go wrong quickly in infants. But further development, growth and maturation build this homeodynamic space as a sort of buffering capacity of the body. If the buffering capability works fine, we will survive; if not, we will die. Of course, things could go wrong at any age, but with respect to aging, this could be due to the shrinkage of the homeodynamic space, which happens during the period of survival beyond the naturally required or essential lifespan of a species assured by evolutionary selection.”

The application of hormesis in aging research and interventions is becoming increasingly attractive and successful. The reason for this is that the research is showing that mild stress-induced activation of one or more stress response (SR) pathways, and its consequent stimulation of repair mechanisms, is effective in reducing the age-related accumulation of molecular damage.

Suresh Rattan, a scientist in the field of the biology of aging (biogerontology), based at the Department of Molecular Biology and Genetics at Aarhus University in Denmark, has spent 30 years researching hormesis, that is, health benefits of repeated mild stress of choice. *Biogerontology* is also the name of a peer-reviewed international journal, published by Springer, of which he is the editor-in-chief. A slight man with a greying beard and a somewhat ethereal intellectual demeanor, this scientist could, at first glance, be mistaken for a yogi. This is a description which, I suspect, wouldn’t please him, as he was quick to inform me, early on in our interview, that despite having roots in India, he is first and foremost a scientist.

Aging was the main topic of discussion at the IAGG Congress in June, where I met Rattan and where more than 3000 scientists from around the globe debated aging in the context of everything from genetics and medicine to urban planning. How we manage the aging process is increasingly important, as an aging global population is having a significant impact on the world’s resources. Living longer doesn’t necessarily equate to being healthy.

The statistics show that the age of our community is rising, especially in the developed world. Currently people aged 60 years and over represent 11,4% (794 million) of the total world population. By 2050, this group is predicted to rise to 22%, or two billion. By 2015, there will be more people aged 60 and over than aged 14 and under. The most rapid increase in the 60+ population is occurring in the developing world, which will see a 225% jump between 2010 and 2050. Statistics also show an individual’s lifespan is linked to lifestyle factors, more than genetics. In fact, science reveals that your lifespan will be determined by your lifestyle accounting for up to 70%, and genetics will determine only 30%. By gaining a better understanding of the aging process, science may be able to help those embrace a better quality of life as they age.

Explains Rattan: “We know aging is not caused by anything: not by an infectious agent or a pathogenic process, or even by specific genes. Aging happens because of evolutionary neglect, a progressive loss of health – at least, in biological terms. It occurs in spite of complex pathways of maintenance and repair, and that is what we need to maintain or even recover.”

Rattan studies aging: a discipline known as gerontology, which is the study of the social, psychological and biological aspects of aging. This is not the same as the study of geriatrics, which studies the diseases of older adults. He says life is a constant struggle between the causes of damage and those that maintain and repair. “What we need to understand is there is no ‘enemy within’ which has the specific evolution-selected function to cause aging and death. This understanding of aging should transform our approach towards interventions, from therapeutic ‘anti-aging’ to maintaining health.

“But what is health?” he asks me. “Ideally, health is a state of complete physical and mental independence in activities of daily living, but in pragmatic terms, health is simply a state of adequate physical and mental independence in activities of daily living.”

Rattan’s work centres on the theory of hormesis, which he believes gives scientists an entry point into dealing with the dynamic response of the body, and the framework within which the body responds to aging influencers.

STRESS OF CHOICE

“**WHEN STRESS IS OF YOUR CHOICE AND IF YOU ARE ABLE TO MANAGE THIS CHOSEN STRESS, IT IS FOUND TO BE GOOD**”

Rattan says we often talk about stress as being bad, but in terms of hormesis, a stress of choice in certain amounts will be good.

“Hormesis in aging is based on the view that by deliberately challenging the homeodynamic machinery, this will transiently stimulate the compensatory, adaptive and reparative processes in the body. The best example of hormesis is exercise. As long as this stress is not costly to the system, you may get certain benefits.

We realise when we are talking about homeodynamic space, what we are talking about is disturbing the system so that the system responds through one or more of these basic molecular stress pathways. This is a requirement for hormesis and aging; the system must respond to one or more of these pathways.”

Various mild stresses that have been reported to delay aging and prolong longevity in cells and organisms include thermal shock, irradiation, heavy metals, pro-oxidants, electromagnetic field, hypergravity, exercise and food restriction. (As Hormesis is also one of the most likely explanations for the health-beneficial effects of various foods and their components, including spices, flavonoids and polyphenols.) The operating principle behind hormesis is that low levels of stress from physical, chemical and biological stressors often result in the functional improvement of cells, tissues, organs and organisms – a phenomenon termed physiological hormesis.

But how much stress is bad and how will we know which is and which isn't, I ask Rattan.

“Constant stress which is not under our control is definitely bad. However, when stress is of your choice and if you are able to manage this chosen stress, it is found to be good. This is the phenomenon of hormesis, and hormetins are the conditions which cause hormesis, and can be physical, mental and nutritional hormetins.”

Rattan believes the most important aspect of stress response (SR) is that it is not monotonic with respect to the dose of the stressor. Rather, it is almost always characterised by a nonlinear, biphasic relationship. The key conceptual features of hormesis are the disruption of homeodynamics, the modest overcompensation, and the re-establishment of homeodynamics.

Rattan likes to use the analogy of physical exercise: “Nowadays, almost everybody accepts that exercise, done at a moderate level, is good, yet it's clearly a stress on the body. Humans need this good stress. Stress can be beneficial, depending on the intensity, duration and frequency of the stress, and on the price paid in terms of energy utilisation and other metabolic disturbances.

“Exercise is a stress, but it pushes you and your body; your muscles work, they ache, your heart rate goes up, you sweat and exert energy. This causes the body to create the response, and after you have finished exercising, in your recovery time, your body replenishes and recovers, and so the cells renew. You also feel very good about it.”

He suggests taking a sauna once or twice a week for

between 15 and 20 minutes, alternating with cold showers, as they do in Scandinavian countries.

Another good stress, says Rattan, is a fever. This is a controversial topic on its own, yet Rattan confirms: “When we experiment in the laboratory, we see the positive effects on cells after we heat them. The cell reacts to the stress, then it recovers and replenishes.”

He describes, too, how even radiation can have a positive effect. “We have confirmed the positive effect of radiation. Yes, we're all told it's bad. However, even radiation, in the correct (small) doses, can have a positive hormetic effect.”

Rattan has many examples to share, such as our obsession with hygiene and being germ-free. “Our approach to making everything too hygienic is bad. The younger generation is not coping in this over-hygienic world, which is why we are seeing so many allergies. The body's cells need some of these influences to respond, but we are restricting this with an over-reliance on hygiene.”

He adds that stress can even occur in meditation, when you are focusing on calming your mind. “Scientists have measured it and observed that when meditating, our stress protein levels increase, a sign that the body is responding to a stress of choice and it will have a physical benefit.”



THE SCIENCE

I ask Rattan how much stress is good. I am hoping he will give specific measurements, but he is honest: “Unfortunately, science is not ready for that precise answer yet. This area is so new that, first of all, we have been providing proof of the principle. Coming down to a specific of how long and what kind is not yet available at scientific level. While a lot of data is there and there are trends, there are still many other considerations, such as the fact that each person is different and will respond differently, so there is still much work to be done to predict the ranges.”

At a philosophical level, Rattan's theories surely raise the point that not everyone can control stressors, or know which are good or bad for them, and in what quantities.

“It's not a perfect world and there will be always be bad stress. However, it is how we facilitate the good stress that balances this

out. We cannot always choose the right kind of stress or not. You can be very stressed when you are not actively choosing the stress, and sometimes you are not going to have control of this. For now, we talk about a starting point being choosing your stress – a stress of choice is always going to be beneficial. And if you are in a stressful situation that you don't choose to be in, you need to find a way to manage it.”

Rattan believes this lies in our attitude. “When we go to gym, we don't see this as stress, but it is; it is just good stress, so it doesn't worry us and we like it. So we should change our attitude to work stress and then we may have a better control over our reaction to it. This is more of a mental attitude and can turn a perceived bad stress into a health benefit.”

I asked Rattan how the scientific community has responded to his research. He confirms grants to further his research and solidify the findings are hard to obtain, as most of the focus is on disease management. “I feel a great support from people as we talk about health, but my job will be easier when ethical committees agree on this approach. The chances of side-effects from this health approach, to stay healthy as such, seem to be very little so far. I think this could be handled relatively easier than the alternatives. Opposition could arise from the conventional, disease-oriented

researchers, as they require a change in their way of thinking. It will also depend upon the structural organisation of the visionary centres and the decision-makers for grants.

“The interesting thing is that social scientists are already writing about health from this view – for example, Colin Farrelly (EMBO Reports. 13(3):2012) and James Shelton (Nature. 493:453, 2013) – but not as many experimental biologists are taking this route as yet. I would also like to stress the fact that there are ministries of health, departments and faculties of health – but there is practically no research on understanding what health is! We need more markers and models to study how the three controlling factors buffer the changes in homeodynamic space. These are some of the current challenges to my vision of personalised health maintenance.

“Supporting health-oriented research is the urgency of our time,”

he enthuses. “The scientific rationale for the need for understanding and defining health is the present crisis in dealing with lifestyle diseases.

The traditional biomedical approach of disease-directed treatments has now come face-to-face with the big challenge of how to deal with physical, mental and social health issues where there are no clear-cut causative agents or “enemies” (such as germs, bacteria, viruses, pollutants, etc). With increased life expectancy and rapidly changing demographic structures, major conditions such as aging, metabolic disorders, depression, dementia, osteoporosis, sarcopenia, incontinence, malnutrition, and several types of cancers are known to be due to the generalised processes of life and their interactive networks.”

He adds that another important sociopolitical reason for the need for having such health-oriented thoughts, in contrast with the disease-oriented views, is the realisation that continuing the disease-oriented approach to health is scientifically and socioeconomic-politically not compatible with the highly desirable future of global health and sustainability. “Several prospective analyses have shown that the prevalent disease-management or disease-treatment approaches are economically, socially and psychologically unsustainable as compared with health-oriented and preventive strategies.”

NUTRITION

During the IAGG Congress, there was much discussion on the benefits of caloric restriction and how this may help slow the aging process. I asked him if he shared this view. He responded that he agrees to a point, that intermittent fasting, once or twice a week, is showing to have beneficial results.

Other nutritional aspects to hormesis include incorporating spices in your food. “I bet you don't know that eating curcumin produces the same proteins in your cells (due to the molecular effect) as when you are active at gym. This is not an excuse or substitute for exercise, but I am just trying to illustrate how knowledge of hormesis can help to enhance one's life.”

He adds that we are now going in the direction of discovering hormetins – hormesis-inducing substances/processes in physical, mental and nutritional terms.

“Lots of things we eat are eventually good, just because they are initially bad. For example, almost all the spices, ginger, garlic, onions, curcumin and other herbs, which don't have any nutritional value in terms of proteins, carbohydrates and so on, are potentially damaging them, and then the homeodynamics of the body naturally takes over to gain the benefit, like physical exercise.”

He says that if you take away the free radicals produced during physical exercise, by providing antioxidants, etc, you lose the benefit of exercise.

“The good effect is because of hormesis – but not daily. Rather every other day. You always get the benefits during the resting periods. So skip some meals. Use other combinations.”

Rattan says nutrition companies are cottoning onto this science, and in Europe there are now vitamin pills with hormetins.

THE MEDIA

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”



But how does Rattan feel about the media's unhealthy obsession with youth, and how does he view his own aging process?

“Personally, I hate the term anti-aging. It's so misleading. I believe taking a healthier approach to health should not be punitive, nor should fear tactics be used to achieve this. People are being made to fear aging and bad health. We have to stop sending messages to everyone saying their bad health behaviour will be punished. People should not feel they have to live a deprived life to be healthy. I believe they can enjoy a healthy lifestyle if they understand the dynamics better and create their own personal mantra for health.”

He adds: “As for me, I'm aging nicely, gracefully and positively, and I accept my life.” He notes that mentally, it seems as if we all stop aging from the age of 40, a time when biologically we actually start the aging process. “It seems that our minds do not visualise that we grow old beyond 40 or 45, at all further ages. Of course, it is in the absence of any serious disease that the mind stops aging when the body begins to age!”

Rattan despises how the elderly become invisible to society. “It's not right. We live in a youth-obsessed society, where there is an unhealthy disregard for people who age. This is why the work of gerontology is so important. We focus on providing a better quality of life as people age, and social solutions for healthy aging. I look forward to my old age. We cannot deny biology. We need to embrace it. We should celebrate old age and focus on how we can maintain health longer over time.”

We're coming to the end of our interview. Rattan's work on hormesis provides a thought-provoking base on which we could develop better health and aging tools, and his approach on how we can use stressors to our benefit is certainly empowering.

And yet despite the hype and human desire that surrounds preventing aging, Rattan's closing comments to me remain firmly grounded in reality: “Science cannot make you immortal. Science cannot perform miracles.”

THE KEY HORMETINS ARE:

Physical hormetins: exercise (running, walking, weightlifting), temperature (hot sauna or cold baths), irradiation (sunlight, solar treatments), needle-pressure (acupuncture).



Nutritional hormetins: food restriction (fasting, low-calorie diet), spices (turmeric, clove, ginger, garlic, onion) and micronutrients (zinc). There are many more nutritional hormetins yet to be identified, and synthetic hormetins yet to be synthesised.



Psychological hormetins: mental activity (reading, puzzle-solving, chess), public speaking, Sudoku, reading a book in a mirror where you focus your attention, meditation and yogic breathing. If you work and have a lot of intellectual stress, this would balance it out.



The value of Rattan's theories of hormesis hasn't escaped the cosmetic industry. Givenchy, one of France's leading cosmetic brands, sought to collaborate with Rattan when its own scientists noticed similar effects of hormesis. Rattan's work had shown skin cells subjected to “stress” in the form of high temperatures for short periods appeared to age more slowly, live longer and function better than those left at a normal temperature, stimulating them to produce protective compounds.

Givenchy sought to create a product that would simulate this stress by using some natural algal extracts – with the aim to encourage skin cells to produce proteins that would help to “heal” and protect the skin. The tests revealed that the product “reinforces tone and elasticity”, and “slows wrinkle formation”.

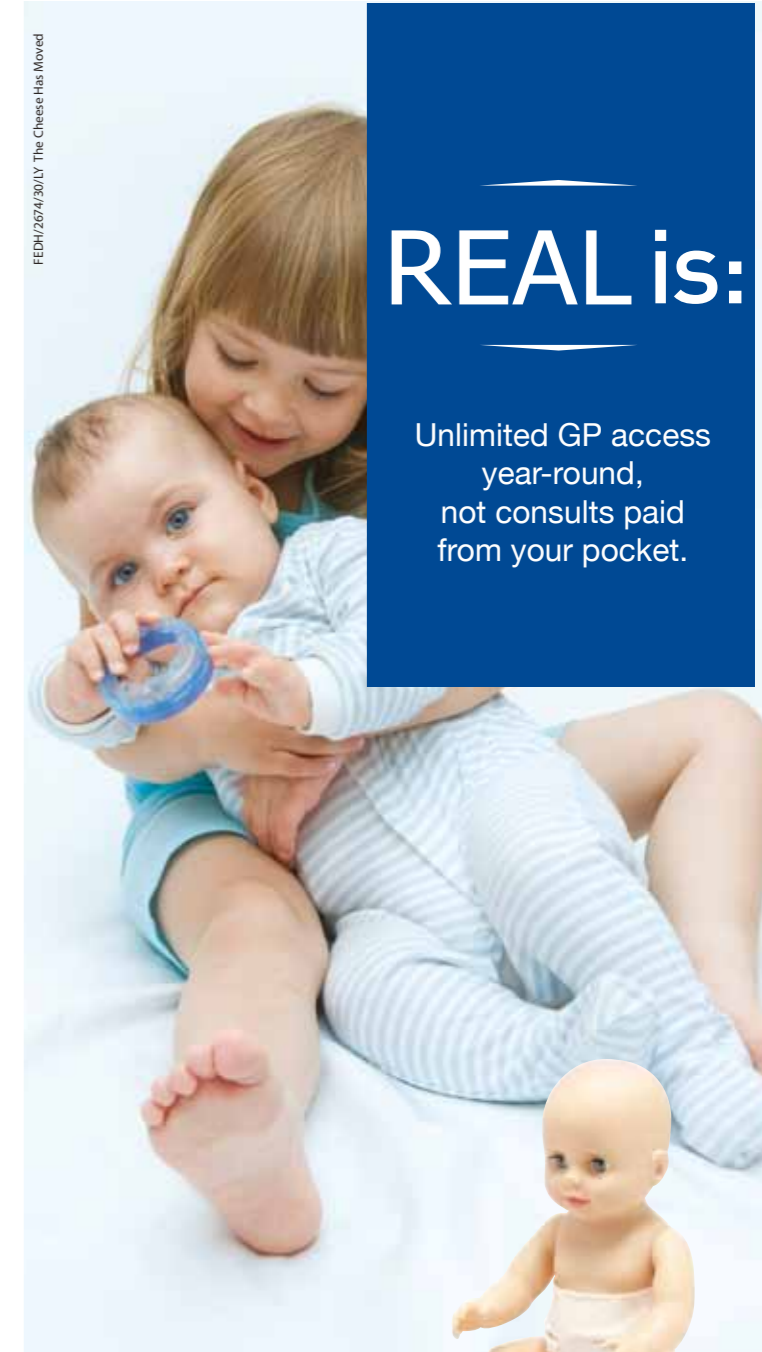
Givenchy launched the resulting product range, Vax'in For Youth, in 2010. Laurent Nogueira, the company's scientific director, said at the time of the launch that the research was still at an early stage. “We know that in order for our products to be credible, we need to carry out longer-term tests on more subjects, and we will do that. But for now, we're satisfied that our studies show that Vax'in is doing something at both a cellular level and at a level which is visible on the skin.”

Vax'in serum was launched in South Africa in July 2011. David White, Givenchy's South African education officer, confirms that Vax'in has fared well in the local market and is now the single biggest-selling product in its skincare range. Internationally the franchise accounts for 12,2% of its total skincare business.

The First World Congress on Healthy Ageing was held on 19 – 22 March 2012 in Kuala Lumpur, Malaysia, and was co-sponsored by the World Health Organisation. It encompassed all aspects of health issues in mainstream, complementary and alternative medicines – including prevention, management, and the latest medical research and healthy aging protocols.

South Africa will host the Second World Congress on Healthy Ageing from 26 – 29 July 2015 at the Sandton Convention Centre in Johannesburg, managed by confex organisers Scan On Show. It will be a global forum for internationally renowned experts, who will address healthy aging issues in the new millennium, and the topics that were addressed in 2012, but with a specific focus on how they apply to the African region. Longevity is the official media sponsor.

For more information on the 2015 congress, please visit <http://www.wcha2015.com> or contact Daksha Vallabh on +27 (0) 11 431 4126 or daksha@wcha2015.co.za. You can also find our more at <https://twitter.com/WCHA2015> or <https://www.facebook.com/2015WorldCongressOnHealthyAgeing>. ■



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