

A portrait of Suresh Rattan, a man with long grey hair and a beard, wearing glasses and a purple shirt. He is smiling slightly. The background is a plain wall with some equipment visible on the left.

A conversation with Suresh Rattan,
University of Aarhus, Denmark

“We Must Come Out of a Disease-Oriented Research”

Photos: Rattan lab, University of Aarhus

For biogerontologist, Suresh Rattan, extending health-span and longevity is a matter of understanding what determines health and how to maintain it in the first place. Consequently, he demands a clear shift of conceptual focus for biomedical research – away from disease towards health.

Lab Times: In your recent publications, you have argued for understanding health and finding ways of maintaining it as ageing-interventions rather than treating ageing as a disease (*Biogerontology*, 13:83-91; *Exp Gerontol*, 48:94-8). Would you like to share your views on why the current disease-perspective of health needs a change and which role biogerontology can play?

Suresh Rattan: My understanding of ageing at the biological level has been through my active research and education for more than 30 years now. This has made me realise that the issues of ageing, age-related diseases and longevity cannot be approached successfully with the prevalent biomedical approach of targeting one disease at a time and trying to either cure it or manage it at best. Ageing is not caused by anything: in the sense, not by an infectious agent or a pathogenic process or even by specific genes. Ageing happens because of evolutionary neglect – so much has been written about it by evolutionary biologists.

Ageing is a progressive loss of health, at least in biological terms, and that is what we need to maintain or even recover. But we are not clear about what health is, in the first place. Even the WHO's definition of health goes like this: “a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity”. This is ambiguous because it intro-

duces another word, “well-being”, without really telling what it is in biological, social and psychological terms.

Quite an interesting start! But before going into more detail we have to clarify: Why “Biogerontology”? Are there other tags for “gerontology”?

Rattan: Well, gerontology, in general, is the study of ageing but from different points of view it can be different. At the clinical level, it is geriatrics and from the sociological point of view it is called social-gerontology; and then there is also psycho-gerontology. But the study of ageing phenotype and mechanisms at the biological level is biogerontology, irrespective of the model systems we use – fruit flies or mice or nematodes or human.

Geriatrics will never deal with ageing in fruit flies, for instance. Actually, the term biogerontology only came into more regular use around 1996 or 1997. When, in 1995, I was awarded the academic degree Doctor of Science in the biology of ageing for my post-PhD research work of about

13 years done at the Aarhus University, I was able to introduce a new lecture-course in our university, with the title “Biogerontology”, which became extremely popular among students in natural science and health faculties. A few years later, in 2000,

when the then Kluwer Academic Publishers (now incorporated in Springer) approached me about starting up a new journal in the field of ageing, the title *Biogerontology* proved to be the best one. This journal deals with both the understanding of the biological basis of ageing and novel interventions at the biological level. Before 1996 or 1997, if you go to PubMed, for example, you would never or rarely encounter the term biogerontology!

The question then is how the subject of biogerontology has led you to think about health and making a change from the disease-oriented thinking?

Rattan: Well, the change comes from the understanding of biology in general and, for me, from biogerontology in particular. From the classical text books 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 two or so decades, we have realised that a biological system is a dynamic entity. It's not by being in the same state but by the same dynamics that biological systems respond, adapt and survive.

This is what I think led F. Eugene Yates in the 1990s to propose the term homeodynamics (*Math Comput Modelling*, 19:49-74). Changes keep happening in the biological

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systems that appear to keep the system apparently static. But 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. But many scientists still stick to the concept of homeostasis and may consider biological systems as machines, which is actually an obsolete notion. I think it is a hindrance to further progress and should be avoided.

So, how does homeodynamics relate to your research? Or how does it help approaching health per se?

Rattan: In the field of ageing, several scientists, including me, think that homeodynamics is the means by which we live and exist. The idea of homeodynamics has led me to formulate the concept of a “homeodynamic space” as the survival ability or buffering capacity of the living systems, which can be the basis of understanding health, ageing and longevity. An apparently healthy child 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 ageing, this could be due to the shrinkage of the homeodynamic space, which happens during the period of survival beyond the essential lifespan of a species assured by evolutionary selection.

How do you define the homeodynamic space of a living system?

Rattan: There are three things that I narrow down to. The number may vary according to different scientists but there are three essential characteristics, in my view. First is the stress response: how a system responds to stress and counteracts or tolerates stress at any age. Second are damage control and damage management. Life is constantly exposed to multitude of damages from internal and external causes and at all levels from molecules to cells and beyond. But very complex and complicated systems work to prevent, control, repair and remove those damages that occur in combination in our body. Damage control is an

important component of the homeodynamic space. And third is constant remodelling, that is, constant adaptation with respect to these damages or changes, corresponding to the age. These make the homeodynamic space and that is what health is. By the way, these three characteristics of the homeodynamic space can also be understood at the psychological and social levels.

What are the positive biomarkers for health then?

Rattan: I don't have a straight forward one-line answer. That is why I'm openly inviting other scientists and thinkers to come up with their ideas for a collective approach. I have tried to develop upon the stress responses from the biological point of view. And what I have listed in my publications – the seven cellular stress responses – may also not be complete. It's a list with respect to immediate and delayed responses to stress. Stress response can be a positive biomarker for health and homeodynamics. As a biogerontologist, working with stress and ageing, I ask, what are the “healthy stress profiles”?

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to the age. These make the homeodynamic space and that is what health is. By the way, these three characteristics

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In general, we would like to see how a cell, at any particular phenotype and age, behaves as it does. A healthy cell can have a multitude of ways of being healthy. We would like to find the range of normal profiles. Since the homeodynamic space is defined on the basis of stress-response, damage control and remodelling for each category, there will be several biochemical pathways.

Is this how your research proposal has taken shape – to demonstrate health?

Rattan: Yes, from a biological point of view – or specifically, from the point of view of biogerontology – I would like to understand what are the limits of the three characteristics of the homeodynamic space and how wide is its range in healthy individuals at different ages. For me, these can be the

biological determinants of health, which can be measured in a demonstrable manner. But, as I said in the beginning, I would

love to hear the ideas of other scientists and thinkers as to how to proceed with this line of thinking.

How do you think, social scientists (or thinkers from humanities) can contribute to define health?



Suresh Rattan

...graduated in 1977 from Guru Nanak Dev University, located in the spiritual centre for the Sikh religion, in Amritsar, north-west India. After a brief stint at the Jawaharlal Nehru University, New Delhi, under mentor Sivatosh Mookerjee, Rattan, swapped the Asian continent for Europe, to begin his PhD studies in the labs of Robin Holliday (who gave his name to the Holliday Junction) and Ian Buchanan at the National Institute for Medical Research, London, UK. He received his PhD degree in 1982. Since 1984, Rattan is affiliated with the Aarhus University, Denmark, starting in the group of Brian Clark at the Laboratory of Cellular Ageing, which he now heads. In addition to science, Rattan dedicates some of his time to classical Indian music. He played the Tabla (percussion instrument) on an album by Danish musician Harry Jokumsen (“State of the Art: Small Town People”).

Rattan: We can already define health! The issue now is to measure health in objective and demonstrable manner. In ideal terms, I define ideal or perfect health as a state of complete physical and mental independence in performing activities of daily life. This is not possible, and no one has it. As soon as we use even clothes to protect from heat and cold, or when we use spectacles to focus our vision, we have lost our independency. So, in realistic terms, what we mean by health is to have adequate physical and mental independency to lead daily life. Here, the term “adequate” is the crucial one and all we need is a set of measurable parameters at the fundamental level of biological organisation to quantify this adequacy.

So, coming to your question on how social scientists can contribute is to bring out the result in terms of adequacy in independency. An elderly person perhaps no longer wants to play competitive tennis or run around as s/he could do forty years earlier. First and foremost all s/he wants is to be able to control and perform basic bodily/hygienic functions, to take care of her/himself and to go about doing other activities in daily life with adequate independence. Adequacy is learnable, a matter of temperament, of value system and ethics. This is also very subjective, psychological and sociological. This is what we also call the quality of life, which is purely subjective.

Biologically I might be perfectly healthy, if measurable. But for other reasons, the quality of my life – like being happy or creative, etc. – might be bad and vice versa! A good example is Stephen Hawking. Biologically he is clearly not healthy. But the quality of life he has for himself and for others is tremendous. This is where – if and when the sociologists and psychologists bring out the results from their research and ideas – they can contribute a lot to measure health from different angles. But, as a biologist, if I can measure health in terms of homeodynamics and homeodynamic space, this could lead to an improved personalised medicine.

What are the challenges for your ideas towards personalised medicine?

Rattan: We need more markers and models to study how the three controlling factors buffer the changes in homeodynamic space. Different cells will have distinct

levels of stress response at different ages or times. How to test these? Which experimental methods or technologies or model organisms can we use?

These are some of the current challenges to my vision towards personalised health maintenance.

We are used to knock-out or knock-down approaches in studying biology or disease mechanisms. In the light of your views it looks like this approach does not work. Am I correct?

Rattan: Knock-out does not work for a health approach. It’s an all-or-none approach we have right now. For example, if someone pushes me under a truck and sees how I die, it’s a knock-out approach. But we try to improve things and processes in



Still knows the inside of a lab
– Suresh Rattan.

biology. So, a titration approach can work. For example, how much disturbance can a body tolerate to maintain its health? To study this, we can try to introduce damage as titrations, say, in 10%, 20%, etc. This is called allostasis or allostatic load – the level of damage control/management. From this we shall see how the systems respond so as to maintain health. By doing so, we will compete with evolutionary selection ‘forces’. Improving something in a pre-ageing body system might have some trade-offs evolutionarily. Otherwise, evolution might have slowed down, or avoided the process of ageing. This is where the damage control concept comes into work. Thus, by this approach, one can keep on having functionality without rushing to death or becoming clinically dependent.

How do you think such studies will involve people? Invasive or non-invasive methods?

Rattan: What our lab and many such labs do are to work with cell lines or animal models. But we need to work more with

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normal humans. So far, we do not have a set of biochemical standards to measure health. So, there should be possibilities for several non-invasive methods. For instance, can we develop a stress profile kit or a strip that can be put into the mouth to get information from saliva – to get results on one’s stress response ability (or level) at that particular time point? Can there be recommendations from those results, like what is the healthy range of stress response profile for that person? This might be one of the technologies to come out of this kind of research. Research is also in progress, for instance, on daily life activities that are matched with functionality. For example, measuring the speed of walking, and some other measures of functionality, seems to correlate with the perspective of one’s dying in the next two to three years at the physiological level.

Don’t you think that even the non-invasive methods will lead to ethical issues?

Rattan: Quite possibly, I don’t deny that. It is the same with any medical research. But we have to promote health to people and tell them what the benefits are of this research. We must not frighten them – if you don’t do this, you will get breast cancer and have to eat broccoli for the rest of your life. No! We can’t do that. The question is to sell health – that “drugs” can be taken to promote health. It is like “teaching ethics by being good *per se*; not teaching ethics by terror”. To involve healthy people for such studies requires reformulation of ethical rules. At an individual level, some incentives might be needed. People need to be educated through the revised biomedical ethics. I must admit, however, that I haven’t thought much about it yet!

Do you have more opponents or supporters of your concept? And what do you expect for the future?

Rattan: 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 opponents. 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 so many experimental biologists are taking this route, 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!

Let's move on to something else. How is your experience as the editor-in-chief of the journal Biogerontology? Can you share some behind the scenes experiences?

Rattan: Interesting and a good move, indeed! Because it's run by a company, it has its own usual economic limitations. But we do not charge anyone for publication. It's a strictly peer-reviewed journal. I should say I have the support of the big publisher who does not measure the success of the journal by money alone. So, in general, it has been a wonderful experience for the past 13 years, to run the journal. I'm able to see the direc-

tion of experimentation and data flow in the field and also, to a reasonable extent, have an influence on them. I am able to promote novel and speculative ideas, even if somebody does not have immediate evidence. This is one of the special features of our journal that it is quite progressive and open towards risky research than many other journals. We do not wait or push scientists for an extensive or a complete study, to wait for years, for a small paper. Rather, we quickly pick up the latest trends in the field so that it can lead to further experimentation.

I also highly admire those scientists who provide free services to evaluate the submitted manuscripts for publication. It's a rather time-consuming and selfless job to do! On an average we receive about 120-130 manuscripts per year and are able to finalise up to 50-60 papers for publication – making a

50-60% acceptance rate. There is no money involved in this process – we do not pay the writers or reviewers.

What other unique experiences or qualities does the journal have – on you or on science, in general?

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generations of scientists, which I'm happy about – honestly! Two things that I can be proud of about running the journal, as an editor-in-chief: bringing a younger generation of scientists into the editorial board, like fresh post-doctoral researchers, or those with three to five years of postdoc experience, besides having senior researchers for several known reasons! On an average, the age-profile of scientists on our editorial board is much younger than in any other journal. I personally approached some senior scientists who were already well-established and were members of the editorial boards of various other journals. I wanted them to point out at least one person from their circle “who was ready for the next generation”. Most of these scientists have been very nice and generous in pointing so and so young members of the board. But I've also been criticised for these moves because

“Biogerontology now has more than 33% of women on its editorial board. This is not a common example seen in scientific journals.”

next generation of biogerontologists.

Another important decision that I made was, wherever I had the choice, I've tried to include women scientists in our editorial board. That might, sometimes, even be unfair to some men but when we do not see many women on editorial boards of journals, except the ones who are already 'famous', I wanted to bring in this group of scientists. So, *Biogerontology* now has more than 33% of women on its editorial board. This is not a common example seen in scientific journals.

VIJAY SHANKAR BALAKRISHNAN

Read more views of Suresh Rattan on academic research, research commercialisation, cosmetics and placebos and on his life in Denmark online in our full Lab Times interview at www.labtimes.org.

Rattan: I'm more of an introvert. But the journal has made me more outward-going and interact with older and younger

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