Biogerontology **3:** 317–324, 2002.

Interview

A global view of the causes of ageing: an interview with Robin Holliday

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My association with Robin Holliday goes back to 1979, when as a young PhD student from India, I joined his labs at the National Institute for Medical Research (NIMR), Mill Hill, London. Robin Holliday joined NIMR in l965, and was invited by Sir Peter Medawar to become head of the newly created Division of Genetics in l970. Already by then, while working on fungal genetics, he had made a major scientific contribution by putting forward the hypothesis about the mechanism of homologous recombination, which later came to be known as the Holliday structure, and which also largely led to his election as a Fellow of the Royal Society, UK. During more than a 20-year period at the NIMR, extensive research undertaken by him and his colleagues resulted in not only the collection of significant data and developing new ideas with respect to the ageing of cells in culture, but also got several students and scientists interested in the important question of ageing. Robin himself has recently recounted the brief history of the Mill Hill School of Ageing in an article published in *Trends in Biochemical Sciences (TIBS)*, 26: 68–71, 2001, and a fuller account appeared in *Experimental Gerontology* 37: 851–857, 2002.

In 1988 Robin decided to leave NIMR for both scientific and personal reasons and join CSIRO, Sydney, Australia, where he retired in 1997. My 3 years of research studentship with Robin, followed by almost 20 years of "from keeping in touch to family-level gossiping" have revealed to me several layers of Robin's life, intellect and personality to an extent that I have now become one of his admirers. For me Robin has also been the source of encouragement and inspiration in starting up this journal *Biogerontology*. I have been very keen to interview him for *Biogerontology*, and we both tried several times to get together in Australia, in India or elsewhere, but each time for one or the other reason we could not make it. Finally, we succeeded on 29 September 2001, and in the not-so-peaceful lobby of the Hotel Paddington in London, I asked him:

Mill Hill school of ageing

SR: From fungal genetics to the question of ageing, that is a big change. How did that happen?

RH: I went from the John Innes Institute to Seattle in 1962 to work in Hershal Roman's laboratory for a year – he was working on the recombination in yeast and I was working on similar problems in *Ustilago*. There they had a weekly journal club and when I came across a paper by Leslie Orgel on the protein error theory of ageing, I presented and discussed it when my turn came round. It drew my attention to the question of ageing, particularly as I knew that ageing in certain fungi was cytoplasm-based, and Orgel's theory was also cytoplasmic. The first experiments I did on ageing were in collaboration with Brian Harrison on my return to the John Innes Insitute. He was interested in ageing and also worked with *Drosophila*, so he suggested that we try and test Orgel's theory. Later I worked on ageing in fungi at Mill Hill. All these results were published in *Nature*.

SR: And did you collaborate with Leslie Orgel?

RH: Yes. I first met him at Cambridge, and then he visited me at Mill Hill in the mid 1960s. Soon after the Genetics Division was set up, he came as a visitor to my laboratory for a year. We had extensive discussions about cellular ageing, and ageing in general. Soon after he wrote an important article in *Nature* on the ageing of human cells in culture.

SR: When did you start working on the ageing of human cells?

RH: When I was invited to set up the Division of Genetics at the NIMR, Mill Hill, I thought of pursuing this question because it would be very appropriate for a medical research institute, although I continued with fungal genetics. Soon after that Dr Arnold Burgen became Director of the Institute, and he was very supportive of our work on ageing. Encouraged by Leslie Orgel, we began to find evidence that senescent human fibroblasts contained altered enzymes. Leslie also had funds for a post-doctoral assistant, George Sensabaugh, and he started to look directly for the misincorporation of amino acids into proteins. We then appointed Ian Buchanan, who worked on the problem of trying to measure protein errors by various means. Several of our papers were published, but they did not give any definitive answers, only indirect evidence. In 1973, Zhores Medvedev came from Russia and he was also interested in protein errors from a different perspective. Zhores did not talk about the feed back of errors as Leslie Orgel did, but he was more interested in the presence and accumulation of defective proteins. He and his biochemist wife Rita Medvedeva joined our research team and documented changes in the chromatin proteins in young and old rat livers. But these studies also did not pin down evidence for or against the particular theory we were looking at.

SR: Were you not by then getting more interested in the wider aspects of ageing and errors?

RH: Round about this time three successive EMBO workshops on accuracy were held, which covered all aspects of macromolecular synthesis. A general principle emerged that to make DNA, RNA or protein molecules accurately enough required investment of energy, and therefore there had to be some kind of trade off between speed of synthesis and accuracy. So accuracy has to be optimised for different organisms, depending on their resources , life style, and so on. In a way that became a general principle, and based on these ideas Tom Kirkwood, who was a biometrician at Mill Hill, came up with his disposable soma theory of the evolution of ageing. This made a lot of sense in the general biological context of what we see around us. We also started to do experiments on the accuracy of DNA synthesis in human fibroblasts. Stuart Linn, a world expert in DNA enzymology, visited the lab and started to look at the fidelity of synthesis in young and senescent human cells. (These results were published in the *Proceedings of the National Academy, USA*.) Later a student, Vincent Murray, extended this work, and the results were published in *Journal of Molecular Biology*. Linn and Murray's results suggested that the fidelity of DNA polymerase declined during ageing, although this was all done with test tube experiments on the enzyme in cell-free extracts. So we also became interested in somatic mutations, but when Alec Morley from Australia came to my lab for a sabbatical, he did not want to use the Hayflick system for these ageing studies. He was a haematologist and he preferred to use white blood cells and measure mutations in those cells. He took blood samples from a wide range of people, quite a few people in the lab, some very old individuals and a few children. He measured the frequency of mutation in the HGPRT gene in the lymphocytes and showed that there was a striking increase in mutation frequency with ageing. That was the first measurement of the mutation frequency with age in the somatic cells in any mammalian system. Then after returning to Australia, he further developed this area and measured other mutation frequencies in man and mouse during ageing. I think he has not got the credit he deserves for that.

SR: Would you say that that has been the general fate of the Mill Hill school of ageing?

RH: No, it is not unique to any one particular group. It happens often that if one particular idea or a theory catches on, then everybody jumps on the bandwagon for a while. Then the fashion changes and something else becomes more fashionable. There was a time when the protein error theory was popular, then nearly everyone thought it had been disproved, so it was discarded. Nowadays free radical damage and telomeres are popular. What is important is that all experimental results are published, and also not forgotten. Hayflick makes the point in one of his reviews that a huge number of biochemical or cellular parameters have been shown to change during in vitro ageing, yet now all the focus is on telomeres, or tumour suppressor genes, or protein kinases. Incidently, many of our more important published results during this period at Mill Hill were reprinted in a book I edited: *Genes, Proteins and Aging* (Van Nostrand Reinhold, l986).

SR: What was the further development of the disposable soma theory?

RH: Tom Kirkwood and I were first interested in the investment of resources for the accurate synthesis in macromolecules. It soon became clear that this was too narrow a view, for example, Tom soon realised that

DNA repair should be included. Later on I proposed that there are in fact many other maintenance mechanisms, which allow organisms to live as long as they do. These include protein turnover, defence against free radicals, the immune system, detoxification, wound healing, epigenetic controls, physiological homeostasis, apoptosis, and so on. They are reviewed in my book *Understanding Ageing* (Cambridge University Press, l995). I like to think that the main contribution of the Mill Hill laboratory or school of ageing is to establish that ageing is all about maintenance. If you maintain things well, you live a long time, but if you do not maintain them well then you live a short time. This of course covers the whole diversity of changes in cells, tissues and organs, and can be considered a universal theory of life which can be applied, if not to all creatures, at least to all mammals, and birds as well. This also means that most important theories of ageing have validity, such as the free radical theory, the somatic mutation theory, the mitochondrial theory, the immunologic theory, and various defective protein theories. It is also important to realise that all those investigators who work on one or other aspect of the various maintenance mechanisms are relevant to the wider studies on ageing. I strongly believe that ageing has a multi-causal basis, and that to understand it fully one has to take a very broad or global view. I also believe we now well understand the biological reasons for the widespread existence of ageing.

SR: Does that get rid of the need of any programme to cause ageing and death?

RH: There has been a lot of talk about programmes and errors as if these were competing theories. But if you think about it carefully, this distinction tends to disappear. The maintenance mechanisms are determined and controlled by genes. So there is no question that genes control the amount of maintenance investment that keeps the body alive and fit. I like to use the example of the teeth wearing down in a herbivorous animal like a horse, where after the teeth have worn down the animal cannot graze anymore and can starve to death. The length and the structure of the teeth are of course determined by genes, but their wearing down is a stochastic processes. So, if you take them together, the differences in the programme and random defects tend to disappear. You can make similar arguments, for example, in the case of cross-linking of collagen in connective tissue, altered proteins in brain neurones or in the eye lens. I also think the general concept of ageing and the eventual failure of maintenance can well explain the different lifespans of different mammalian species or birds. There is also evidence that maintenance mechanisms are more efficient in long lived species. For example, the work of Alec Morley shows that somatic mutations accumulate much faster in mouse than man.

SR: So, genes are needed for all those maintenance processes, but we don't need genes to switch off those processes . . .

RH: That is right. The point is that it is useless to keep an organism going forever, because you have to invest enormous resources. It is useless because animals in a natural environment usually die from starvation, disease or predators, and rarely from old age.

SR: As an experimental gerontologist, you have extensively used the system of cells in culture to address the question of ageing. But many doubts have often been raised against the validity of this system. Do you think that this system has proved to be useful?

RH: The early doubts were about the very fact that the cells became senescent, and people said that you were not growing them in proper medium etc. I think that was effectively dealt with by a number of experimentalists including Len Hayflick himself (see interview with Hayflick by S. Rattan, published in *Biogerontology*, Vol. 1, No. 1, 2000). It is well established that their ageing is a genuine intrinsic process which has to be cumulative and definitive. There was also controversy on whether this was an appropriate model to investigate ageing, and it was Hayflick's initiative to spell out that it would be a good experimental system at least for the study of cellular ageing. That was then very widely accepted and hundreds and hundreds of papers were published. What has happened very recently is quite unfortunate in the sense that decades of work done on this system has been forgotten and everyone is now talking about immortalization and the genes involved in immortalization. A lot of these people seem to ignore everything that went before. They tend to focus on a few molecular aspects and forget the general principles. A lot of cancer researchers came into the field and promoted the idea that this limited proliferative capacity of normal diploid cells was a kind of tumor prevention mechanism. But I don't fully agree with that, and also the data show otherwise. Take chicken cells for example: cancers in chickens are frequent, and these cells are not immortal when

cultured. Although the division capacity of chicken cells is not that large, it is sufficient to produce the cancer and kill the animals. I don't think senescence is the defense against cancer. There are several other very tight control mechanism that prevent human cells from becoming immortal or tumorigenic. The relative extent of tumour development in man is much lower than that in rodents, whereas normal human cells have much larger proliferative capacity than rodent cells. I do not want to imply that immortalization of normal cells is not a very interesting process. Tom Kirkwood and I developed a theory about that, which was successfully tested, particularly by Lily Huschtscha, but although this was published in *Science* it has so far been ignored.

SR: But can we still learn more about ageing by using the cell culture system, or has it been exhausted?

RH: No, there is still a lot to be done. However, the telomere theory has become so overriding that not much attention is being given to anything else. For example, I am interested in DNA methylation, and it has been well documented that as the cells go through their replicative lifepan, the level of DNA methylation goes down. That is a kind of a replication clock, but that has been completely ignored in recent years. When you immortalize cells by the addition of telomerase as some laboratories claim, then what happens to the DNA methylation? This is never discussed. There must be some connection between the methylation of DNA and the maintenance of telomeres.

SR: I want to find out a bit more about the Holliday junctions; who coined this term, and are they in any way relevant to ageing?

RH: I am not sure when exactly this term was first used or who coined it, but it would be from about the mid 1970s onwards that more and more people started calling those homologous recombination intermediates Holliday structures, or junctions. I had personally suggested the term H-structures for them, but that did not catch on. As regards its relevance to ageing, I am not aware of any specific studies on that, but we do know that sister chromatid exchanges occur in cells and I think that may be the result of a DNA repair mechanism, involving homologous recombination. There is another context where recombination may be important. We know that germ line cells are potentially immortal, and the developmental programme has to be properly renewed. However, I suggested in l987 that epigenetic defects can be transmitted from one generation to the next (*Science*, Vol. 238, pp. 163–170) and there is now more evidence for that than there was then. In the same paper I proposed that recombination at meiosis may have an important role in removing DNA methylation defects. It was work on fungi that lead me to the Holliday structure, and interestingly, recent work on fungi in Jean-Luc Rossignol's laboratory has demonstrated important connections between recombination and DNA methylation.

Ageing, disease and anti-ageing therapies

SR: In ageing research, many people are stuck with doing research on age-related diseases. Do you think we need to come out of this disease model and better find out what normal ageing is?

RH: The health of old people is a very important and central question. A lot of medical people talk about the so-called natural ageing, whatever that is, and the age-related diseases as something separate from natural ageing. I think that is the wrong way to look at it. The body is unable to maintain itself and when different parts of the body go wrong at some stage that becomes the disease, especially if that malfunction is somewhat premature.

SR: But do we need to do research on each disease separately or do we need to develop common research programme under the framework of the biological basis of ageing?

RH: That is the way most doctors look at disease. Whenever there is any particular disease, they tend to treat that specific disease, and ignore the fact that other parts of the body may be failing. Of course the biomedical field is so huge that each specialist is an expert in only one disease, and if something else is wrong a different specialist is called in. In my opinion there needs to be a whole re-appraisal of the field of age-related disease, and much more emphasis on ageing research. What is important is to look for the origin of each disease and then try to prevent it from happening. Prevention is realised to be very important for many diseases, but this is not realised so often for many age-related diseases. I have in fact written several articles on this and related issues. What we need is much earlier diagnosis of the onset of these diseases and then we can perhaps develop methods to prevent its occurrence or at least slow down its progression. So, if we want to treat or

prevent Alzheimer's disease, we need to know what happens in the brain much before the disease appears, and that is ageing research. Of course it is important to treat the disease, but it is even better to prevent it from happening. Huge amounts of money are often being spent during the last three months or so on keeping the body of an elderly person alive, even though other parts of the body may be failing anyway.

SR: Would you take a position here that at some stage that kind of expenditure should be stopped?

RH: Well that is happening in some ways today where doctors take decisions whether to stop or to continue the treatment. Also, it may not be possible to treat everybody equally. There is also the question of the attitude of the patient. I think in Europe, people are more willing to accept the fact that they are getting old and weak, and they worry more about being a burden on others. In contrast, many Americans want to live as long as possible, and that is why there is more dependency on expensive high-tech machines and medication. Certainly, the ever increasing health budgets in developed countries cannot be sustained indefinitely.

SR: What do you think of the anti-ageing research and its present day trends?

RH: Again, there is this difference in viewpoint. It seems to me that scientists in America seem to think that working on ageing means trying to prolong the lifespan, and then some of them make claims that they will be able to do this. The public and the media love it, but it will eventually affect the credibility of those scientists. We have to realize that ageing is built into the very fabric of life, and that we have a limited lifespan. I don't think there are going to be any pills for that. Also, all the talk about stem cells and replacing body parts is fine for people with many years to live, but not for the elderly, where several parts of the body may be failing. All these treatments will be very expensive.

SR: But what about cosmetics? There is a multibillion dollar industry based on big claims for anti-ageing products . . .

RH: Most people will agree that lifestyle is an important factor for having a long healthy life, and generally looking after your body is an important factor. But that is not the same as cosmetics. However, there may be some compounds which have some beneficial effects on the skin which people like to use, but those are not going to make them live longer. They may feel better or happier for a while. There may be some compounds that do have good effects on cells. For example, carnosine, a dipeptide on which I did some experimental testing, increases the lifespan of human fibroblasts in culture. Those results have been published in scientific journals. This compound is being marketed in certain cosmetic products, but I am not involved in that and I don't make any exaggerated claims about it. All I am prepared to say is that it has a better chance of being effective than many other anti-ageing products on the market.

Literary writing and the purpose of science

SR: Since your retirement from CSIRO, you have started devoting much time to writing scientific and science-based stories and novels. What has inspired you to do that?

RH: That is an interesting question. Actually, during the early stages of my scientific career I found it quite difficult to write and I was very slow. I know that many scientists hate writing because it is much more enjoyable to do research work, and many of them keep postponing or may never write down the results of their own work. But sometime after I had published about 50 papers, perhaps in the mid l970s, I started to find that writing becoming easier. Finally, I discovered that I had actually started to enjoy writing. So since my retirement I have written several scientific articles and some non-scientific stories and essays. Writing has become an enjoyable relaxation for me.

SR: What kind of a reader do you have in the back of your mind when you are writing?

RH: I am not trying to write bestsellers, for sure. I am writing about things that are interesting to me and hopefully are interesting to other people. Unfortunately, in the field of popular science a particular type of book has become dominant, which is one that is informative about science to some extent, but also entertains the readers at the same time. These books that are written to entertain are full of anecdotes, metaphors, stories and maybe a bit of colourful autobiography, and that is what the reading public seems to like. But that is not the way I write. I will give you a better example. Peter Medawar wrote a lot of books, mainly collections of essays, and he was generally recognized as a superb writer of prose. His choice of phrase and the use of words is brilliant, but he

also took seriously whatever subject he was writing about. He did not need to use all this ornamentation and decoration. Nowadays books about science are not like Medawar's, but he is a very good model for me.

SR: But can't we combine science and entertainment if that brings science to a large number of people?

RH: There are some good scientists writing books which have brought their field to a wide public, and Richard Dawkins is one. The problem is that there are now a lot of popular books about science written by poor scientists, who may not know much about their field. Unfortunately, the public may not know that they are being misinformed in these cases. The field of ageing is plagued by such books. One of my interests is the real answer to the question 'what is science for?' When I started doing research, it was a golden age for science. My justification of working on genetics was that I thought that genetics was an important subject and we should find out as much as we could about it. In those days, genetics was not that widely spread in the academic or scientific world, and was regarded as a somewhat specialized field. It is very interesting that with the revolution in biotechnology, now genetics is everything, and everyone knows, or think they know, about genetics, genes, DNA and so on. But that is not enough. For me, the ultimate aim of science is to fully understand the human being; and what characterizes the human being is his brain and his ability to reason, to create language, tools for communication, art, science, civilisation, and so on. So, the most complicated and most important biological object on this earth is the human brain. I assume then that all roads in biological science then lead to the goal of understanding the human brain, its action, its learning ability and its interactions. I think that ultimately that will lead to the understanding of human behaviour, emotions, intellect and other aspects of human life. People talk about replacing organs with stem cell technology or creating bionic-man and artificial intelligence, but none of them ever talk about what the situation will be when we fully understand how the human brain works. That is what I like to write about, and that is what my novel *Slaves and Saviours* is largely about.

SR: Will understanding the brain change the way human beings live and interact? Will it affect human virtues and ethics?

RH: Let me answer by giving you an example. Everyone wants their children to be educated well, but the way we teach has not really changed for a very long time. If we were able to teach children in such a way that already at the age of nine they can learn and perform like children of twelve or more, I think most people would like their children to have that kind of education. We already know that humans have huge learning potential – much more than we can usually teach them. If we were able to realize that potential, people would become better in all sorts of important ways, and we will not have to argue about relatively trivial matters, which is what often happens these days. Nature and nurture is a sort of classical argument for which a change in emphasis has occurred in the last several decades, yet we certainly still do not have all the answers about the interaction between genes and environment. That is definitely a key question for future societies.

SR: Do you mean to say that mechanistic answers of science can really affect people's behaviour? Look at what has been going on all around during the last hundred or more years when science has also developed so much.

RH: People do catch up with science sooner or later, and this is shown particularly well from advances in biomedical science. Most people accept recently developed treatments, or facts about good nutrition. Suppose we found a way of curing dyslexia – then surely it would be accepted. Early diagnosis of serious conditions such as cancer or Alzheimer's disease and prevention of their further development would be huge breakthroughs. Of course there will always be suspicion of some new scientific advances, and GM food is a good example of that, but in general people do accept scientific facts and behave accordingly. If you are asking about the depressing international situation, violence and wars, and so on, then I agree that science has not improved that at all. However, I think in many countries, people are much more compassionate and humane than they used to be, and hopefully that will continue. Education and knowledge are very important, and knowledge comes from science.

SR: Will science ever be able to get rid of people's religious beliefs etc.?

RH: After the publication of Darwin's book on natural selection, there was much argument because religious people realised that it challenged many of their beliefs. Yet in the 100 years or so after that the discussion has largely died away and at present many people believe

that these two views are not incompatible, and can even complement each other. I think you will also find that many religious people accept that the earth is ancient and that evolution occurred, but then say it is all part of God's plan. I don't believe that at all and I think that there is a fundamental disagreement between science and religion, and one day in the future that disagreement might emerge again. I think that people will change, but they are changing in some countries much more than in others. Let me be a bit more specific. The whole discussion of the ethics of working on embryos is an example of very muddled thinking, because people who set themselves up as ethicists often do not have any special qualifications. They just decide to be ethicists. But as soon as you realize that cells are just made up of chemical molecules and there is no soul or spirit and no vitalism there, then all those ethical concerns about the use of stem cells just disappear. Politicians are also very muddled in these things. They tend to pay lip service to religion and they like science. This was shown very clearly by President Bill Clinton when the completion of the human genome was announced. He said something like "The DNA sequence is God's gift to man," and it was also said that "until now only God knew the sequence of human DNA." These were very stupid statements and show enormous ignorance of evolution and how evolution works.

SR: And then he has two senior and powerful scientists standing left and right to him, and they smile and they clap and stay quiet and thus endorse it! But, I also want to ask you about who are the slaves and who are the saviours in your novel?

RH: Society becomes polarised with the establishment being religious, and the Godless scientists setting themselves up in centres of excellence where they do fundamental research, particularly in neurobiology. They regard themselves as slaves because they have a lower standard of living, and are to some extent ruled by bureaucrats who are not scientists. When the scientists make important advances in understanding the human brain and behaviour, these impact on the rest of society and become accepted. I have already mentioned the example of education. Anyway to cut a long story short, the scientists eventually come to be regarded as saviours. In a way this situation exists today. Scientists are put to work to produce, for example, pharmaceuticals which make a lot of money for the companies concerned, but they usually do not get the money themselves. In a sense they are slaves and are regarded as important technical people and are not thought to be important for their contribution to society. It is also thought that given the right technology and facilities anybody could do that job, and society at large does not realize that science progresses by intellectual effort and creativity. Most people do not understand the difference between science and technology. The common view is that scientists wear white coats and they do genetic engineering and other such things that people do not necessarily like. This view of the scientists is very one sided and that is its slave aspect. The saviour aspect is when people realize that scientists create new knowledge for the benefit of society, and new ways to prevent or treat various nasty diseases. Public at large do not really understand that if you want real knowledge about the world, then you have to use scientific methods. People are often totally ignorant of the history of science and the contribution of science in making social progress. Also, the view that the best scientists are intellectuals is not at all common.

Sufficient recognition?

SR: Considering your range of thought and ideas-based contributions in the fields of genetics and ageing, have you been considered and accepted as an intellectual by the scientific community?

RH: To some extent, but also perhaps somewhat eccentric, and I can see that in many ways I have not been accepted into the scientific establishment. One way of looking at it is by going back to the recombination work. It took about twelve years for people to take it seriously, and after that it was cited much more often and now it is recognized as a major contribution. The other area I was involved in, apart from ageing, was the concept of epigenetics and together with a brilliant student, John Pugh, published in 1975 new ideas about DNA methylation and gene expression. Not much happened for a while, and there were just a few labs that worked on it, but by the end of the century, that is after 25 years, epigenetics became respectable, and the proper credit is sometimes being given. Unfortunately, the young students and scientists have very little sense of history, and perhaps that is one reason that I am not acknowledged because people do not know where the idea came from. Once at an ageing meeting someone said: 'Are you by any chance related to the Holliday of the DNA recombination structure'!

SR: Maybe people also become frightened of a thinker and an intellectual like you who often do not have much patience for other people's limitations . . .

RH: You may be right, I do expect people to know more than they actually do.

SR: Finally, are you satisfied with yourself as a scientist?

RH: In this age of specialisation, you are supposed to be an expert and specialist in a certain field, but I have never gone along with that view. I have worked in three different areas and that makes everything more interesting, at least for me. I think it is too dull to be a world expert in one specific area. Of course, many people will say that there is now too much knowledge to assimilate enough in different fields. However, what has to be done is to sift through a very large amount of factual information, and extract what is important. I think the field of ageing is an excellent example of that. There is a huge body of information about differences between young and old animals, or people, and a lot of that cannot be interpreted easily at present. However, if you have a broad overview, the biological reasons for ageing become very clear, and also you realise that work in other fields, such as DNA repair, the immune system, protein turnover or detoxification are very relevant to ageing, because loss of effective maintenance is what ageing research is all about. I like to say that many scientists are examining single trees, and they cannot see the whole wood. Lateral thinking, making many connections between different areas, and then formulating new concepts or ideas is the most interesting for me.