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Interview

'Just a fellow who did his job . . . ', an interview with Leonard Hayflick

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Anyone who knows anything about aging also knows, or should better know, what the Hayflick limit is and what the Hayflick phenomenon is. The discovery of this phenomenon in 1961 is an excellent example of the Kuhnian notion of paradigm shift. The stage was then set for systematic experimental studies to unravel the biological basis of aging. We have come a long way since then – or have we? In order to find out more about this, I had an opportunity to meet Dr Leonard Hayflick during the annual meeting of the British Society for Research on Ageing, held in London on July 16, 1999, where Dr Hayflick had also come to receive the Lord Cohen Medal for his contributions to the field of biogerontology. Amidst a busy lecture schedule and a waiting journalist from the BBC, we were able to find a peaceful corner in the Board meeting room of the Charing Cross Hospital, where I switched on my tape recorder . . . .

The big shift

SR: Let us start from the beginning: as far as I know, before 1960 you were very much in the forefront of mycoplasma research in relation to arthritis, so how did this shift from mycoplasma to cellular aging occur?

LH: I attended the University of Pennsylvania first as an undergraduate, then as a graduate student pursuing a Master's degree at first. My major subject in the university was microbiology, and I had a fundamental interest in bacteriology. After I graduated with my bachelor's degree, I went to work at what was then called Sharp and Dohme, which was then taken over by Merck, and Merck, Sharp and Dohme developed out of that. I then realized, having not appreciated this fact earlier, that I did have the intellect to obtain a PhD. I decided to go back to Penn and pursue a Masters and PhD degree. One of my friends at that time, who was in the Department of Medical Microbiology at Penn, which is the department that I chose to apply to, was working with the mycoplasmas. These are very interesting microorganisms – the smallest free-living microorganisms – and I decided that I would like to work with them. So I gained admission to the department and pursued a research project using those organisms when my chief, who was a very young fellow, returned from one of the first courses in cell culture given in the United States. He returned full of enthusiasm about cell culture, and tried to convince me to pursue a research problem having to do with cell culture . . . .

SR: Who was this . . . ?

LH: His name was Warren Stinebring who, unfortunately, is now dead. Warren was such a young Professor that my responsibility on paper was not to him, it was to Stuart Mudd, a very well known microbiologist and Chairman of the Department of Medical Microbiology. So it was my young boss returning from this course full of enthusiasm who tried to induce me to become interested in cell culture. I obtained my Master's degree working at the Wistar Institute, which is affiliated with Penn, and studied the mycoplasma etiology of middle ear infection in the Wistar rats. After a period of time I became aware that I would be better off succumbing to his pressure to do a PhD project with cell culture. So I compromised and decided to do a project on the behavior of mycoplasmas in cell culture. This preceded the discovery of contamination of cell cultures with mycoplasma. So my interest in cell culture resulted from gentle persuasion. But I began to enjoy using the technology and then it became fascinating. I ultimately received my degree, and accepted a post-doctoral position at the University of Texas, where I worked with one of

the leading personalities in cell culture in the world, Charles M. Pomerat.

SR: So, you got your PhD from the University of Pennsylvania, in which year?

LH: In 1956, in Medical Microbiology.

SR: A year before I was born ....

LH: That makes me feel very uncomfortable!

SR: No, no, no, that gives me encouragement that I have been in your footsteps.
(and we are engulfed in our laughter!!)

LH: In any case, I was awarded a post-doctoral fellowship to study under Charlie Pomerat at the University of Texas, Galveston. He was a remarkable person, and the most unusual personality that I have ever met. Unusual in the sense that he had a prolific intellect that included expertise in anatomy, neurobiology, cell culture, marine biology, architecture, art, food preparation, and he was the best lecturer I ever met. After two years, I was contacted by Hilary Koprowski who by then had taken over the directorship of the Wistar Institute in Philadelphia, and induced me to return to Philadelphia to join the Wistar Institute at its new re-birth. It is the oldest biological research institute in the US, and enjoyed a renaissance once he took over. I was hired to run a cell culture laboratory. In addition to running that laboratory, my responsibilities included a research project directed toward investigating whether or not human cancers have a viral etiology. I was working on that project while simultaneously working with mycoplasmas which were still of great interest to me. Through a series of events that I won't relate in detail now, I also discovered, in the same year that I discovered the finite replicative capacity of normal human cells, the etiology of a very common human disease which in the US is called 'walking pneumonia'. It is properly called 'primary atypical pneumonia'. This is a common ailment, which had been thought to be caused by a virus, but I discovered that the etiological agent was in fact a mycoplasma that ultimately I named *Mycoplasma pneumoniae*. This is the only mycoplasma proven definitely to be the etiological agent of a human disease.

As I indicated before, I had also begun to work on the cancer research project, which necessitated the growth in culture of human cancer cells in order to make extractions, in the very primitive way in which this was done in the late '50s and early '60s. My plan was to put the cancer cell extracts on to normal human cells to see if normal cells changed in any way. We were searching after all for viruses. We wanted to use as our normal cells, the cells from human fetuses because at that time it was very well known that the tissue from adults frequently contained garden-variety viruses like adenoviruses, herpes and others. But, these were rarely found in human fetal tissues. We obtained human fetal tissues from a local hospital and from Sweden where surgical abortions were legal, and where we had connections with some scientists in Stockholm. So, we started to grow cells from human cancers and from normal human fetuses.

After about a year or so of doing this I realized that despite the fact that human fetal tissue arrived in the laboratory at random times, all of the cultures were dying after about 50 subcultivations. This was itself not unexpected because I had been taught that cells will die in culture because we do not understand how to grow them properly. But, what struck me about my cultures was that those that were dying were the ones that were in culture longest despite the fact that I had one technician using one pool of media and one pool of glassware on all of the cultures. Nutritional inadequacy was inconsistent with my observation that only the cultures that were growing longest had stopped dividing. That was the inconsistency that tipped me off to what followed.

The paradigm shift

LH: I began to pursue this observation because it was very strange, and I pursued it to the point that it involved my full time attention. In fact, the original project on cancer biology was dropped, and fortunately my results with the normal human cells were so striking that my boss had no objection to my continuing to work on this observation. That was very fortunate for me because at that time there was a great deal of money available in the US for medical research, and following unusual results not written into grant proposals was easy to do. Today, if you do that you would be flirting with a jail sentence for using government funds for unapproved purposes. I did a number of experiments that proved to myself and to my colleague Paul Moorhead that my observation was

not an error. I had worked with Paul initially at the University of Texas, and managed to bring him to the Wistar Institute. He was one of the first cytogeneticists, and he and I worked together for several years. One of the things we wanted to prove was that these cells were normal. By this time the normal human chromosome number had been discovered. So, Paul did the cytogenetics and we discovered, as we had expected, that these cells were normal cytogenetically. We did many other studies that were reported in our first paper, and determined, at least to our satisfaction, that the cells had stopped dividing not because of any accident or ignorance about the culture media, but because of some internal clock. That is the long answer to your short question.

SR: But you insisted on pushing this interpretation that there were intrinsic reasons, which was going against the dominant paradigm of Alexis Carrel at that time!

LH: Exactly!

SR: How did you dare to do that? About a year before you, Swim and Parker had published almost similar curves but they reached the conclusion that there was something wrong with their methods that prevented cells from dividing forever. Although Dr. Peyton Rous first rejected your paper from publication in the Journal of Experimental Medicine, *and then later it was published in* Experimental Cell Research, *what made you stand by your observations? Where did this conviction come from? Can you look back into your bringing up?*

LH: I would not have the conviction to stand by my interpretation of the results had it not been for the fact that the experimental results were very definitive. I won't go through all the experiments because there were many that were done. But, one experiment that I usually emphasize is the one in which Paul and I mixed young female cells with old male cells. By young I mean low population doubling level. We mixed equal numbers of female cells at the 20th population doubling with male cells at the 40th population doubling level. The limit for both was 50 doublings. We maintained these mixed cultures and found that the mixture stopped dividing when the youngest component stopped dividing. Therefore, the argument that media or viruses or some artifact of culture could explain this phenomenon is untenable. Another experiment that what we did and that does not appear in the published paper because of its unorthodoxy is this: I decided to challenge the grey eminences in the field who told me that my culture conditions were inadequate, by sending to them a culture of my human diploid cell strain WI-26 at that time, and telling them that the luxurious culture of human fibroblasts that I am sending to you will stop dividing in six months time. And so, in six months the telephone rang, and they said that their cultures had stopped dividing. I felt that if I had made a mistake then I would go down in flames with the best people in the field. So Paul and I decided to write the paper describing our observations. However, we were still left with the question of interpreting the results. I knew that for the previous 60 years (cell culture began in 1900) it was believed that cells put in culture always have the capacity for immortality. This had profound implications in the field of aging, because if what was believed for the first 60 years of the twentieth century was true then aging has nothing to do with intracellular events. It has only to do with extracellular phenomena. Cosmic rays were invoked at that time as causes of aging, and changes in the ground substance, or anything you can think of that is extracellular. So, this was a major shift in understanding with respect to aging that I was suggesting. I was now focusing attention on the behavior of the cells themselves, and on an intracellular counting mechanism specifically. And I was very well aware of this. We had eliminated other potential explanations. One was simple dilution of some nutritional factor that could not be synthesized in vitro but only in vivo, which we put to rest simply on mathematical grounds.

Human vaccines in WI-38 cells

LH: Our paper contained two other very important elements: one was our demonstration that these normal human diploid cells had the most exquisite sensitivity to human viruses known. They still do. By this time the poliomyelitis vaccine was becoming accepted and it was also becoming apparent that the primary monkey kidney cells used for the production of poliomyelitis vaccines were contaminated with unwanted viruses whose behavior in human beings was not understood. This was a real threat. By this time we had established that cell strains, for example WI-38, were absolutely free of indigenous viruses, and therefore were much safer than monkey kidney. Not only that, monkey kidney was permitted for use only

as a primary culture. I pointed out that human diploid cells could be frozen at low passage level, studied for years to prove that they are safe, and then used for vaccine production. You cannot do this with primary cells. For the first time we introduced the concept of characterization and standardization into cell substrates used for the manufacture of human biologicals. It took ten years of struggling to have these concepts accepted. Now these concepts are the foundation of the biotechnology industry. This in itself was an enormous practical advance but it took ten years for that to be accepted by the FDA where it was mostly delayed for political reasons. In fact, the first licensed vaccine produced in my human diploid cell strain WI-38 was produced in Yugoslavia and later in the UK, Germany and Russia, and finally in the USA in 1972. The problem of having normal human cells accepted for use as substrates for human biologicals has as much a history of antagonism and emotional grief on my part as does the acceptance by the scientific community of the finite capacity of normal cells to divide. People were dying during that period of time because there were several monkey viruses that caused deaths in handlers of monkeys and their tissue cultures. About 20 people had died handling monkeys and their kidney cultures during this period of time, even when there was continued terrific resistance to the use of normal human cells for vaccine production. The reasons for that involve such things as personality clashes, ego, politics and economic concerns. In any case, the outcome of that is that today virtually every vaccine in the world is produced in my WI-38 cell strain or in similar cells. Hundreds of millions of humans have been vaccinated with products made in WI-38 or similar strains with no evidence of a safety issue traceable to the cell substrate.

SR: That is perhaps a much bigger practical application and contribution to science than is the aging story . . . !

LH: That is absolutely true. Almost one billion people worldwide have received and still do receive vaccines produced in my cells which are totally safe and efficacious.

Strength of character and the law suit

SR: One aspect of your character as a person that comes out of both your work regarding the limited proliferative capacity of cells, and later on with your struggle with NIH about the ownership of cells, is that you have a very strong personality. What makes you so strong?

LH: Well, I can't tell you specifically. I can only tell you that my upbringing is probably the key. As I indicated earlier, the only reason that I ever take a strong position is when I am absolutely confident that the scientific data and the reasoning behind the interpretation are sound. In all these cases that is how I felt even when I faced the NIH and brought a lawsuit against the US government. I felt absolutely certain that I was correct, and in fact as events have unfolded, my position has been shown to be correct and ten years ahead of its time. The NIH accused me of having stolen government property and selling it for personal gain, which is, of course, a criminal offense. Today if you don't do what I had done, which was to claim intellectual property rights in WI-38, or some other biological entity, you are a failure in microbiology or cell biology. You are a total failure if you don't own a patent, if you don't have a commercial relationship or if you have not exploited something that has come out of your laboratory as a result of support from tax payers' grant funds. My lawsuit against the US government was so successful, that in ten years even NIH employees can now enjoy a maximum of 100,000 dollars over their salary per year for something they have discovered in a government laboratory, funded by taxpayers. That would have been unthinkable before my legal victory. People have made this observation, and I think it is correct, that had we not won our lawsuit, the biotechnology industry would be much different than it is today. That is because the biotechnology industry is based upon the principle that biologists have intellectual property rights. Prior to my lawsuit that principle was understood and exploited by physicists, electronic engineers, and software writers, but academic biologists were the last group in science in the US to turn 180 degrees from having their skirts soiled by financial interests to becoming entrepreneurs. Now that behavior by biologists is applauded and celebrated. When I became the first one in the US to claim intellectual property rights, I was branded a criminal. I was brought up to be independent and to have confidence in whatever I found that was demonstrably correct and true.

Humble beginnings

SR: That is not a typical Jewish family bringing up where you are taught to respect tradition, to accept ....

LH: I don't think religion has anything to do with it. My mother and father were very liberal. They left me to do pretty much whatever I wanted to do because they had imbued in me the difference between right and wrong. I had the usual childhood exploits that all of us have, but nothing particularly striking that would immediately come to mind. But, my commitment to truth and justice was foremost. I take enjoyment in challenging dogma. If there is anything that I challenge, it is orthodoxy.

SR: Is it a reaction to parents or is it due to encouragement from them?

LH: Oh, it is encouragement, absolutely. My parents encouraged freedom. My father was not a formally educated man because he was forced to work all his life. When he was seven or eight years old he drove a horse and wagon and delivered dairy products from his mother's store in Philadelphia. He didn't go farther than the 7th or 8th grade. He then worked in a dental laboratory and became an expert on the design of most complex prosthetic devices. He eventually went into business for himself, but he never made a lot of money. It was in his later years that he felt a little bit more comfortable, but by no means wealthy. My mother came from a struggling family as well. So struggle was always a part of our background. I grew up in the depression and can recall when my father walked to work from suburban Philadelphia to the center of the city in order to save 15 cents trolley fare. So, being brought up in the depression has a lot to do with my work ethic, my belief in myself, and that I should have confidence in what I think is true and correct as long as it is demonstrably so. I have always had those traits.

Biogerontology as a mature science

SR: You are most well known for your contributions in the field of aging; and aging research is one field where an immediate response from the public is "...wow lot of money ... ". What do you think of the present trend.

LH: I never had that impression. Of course there is a hugely successful exploitation of the public's ignorance of scientific truths, which around the field of aging goes back centuries. One could forgive the lunacy practiced three or four hundred years ago when not as much was known about science and about seeking the truth using the scientific method as we know today. But the lunatic fringe is certainly more present in the field of aging than it is in any other biological discipline, which is a perennial problem. When I entered this field, to declare publicly or even to your colleagues that you were working in the field of biogerontology or aging research was tantamount to committing professional suicide. So you called yourself something else, like a cell biologist or physiologist or whatever. I was doubly damned because cell culture in which I worked was considered to be a black art, and gerontology was considered to be a black art, and the combination was tantamount to having two strikes against you from the start.

SR: Has that situation changed for aging research now?

LH: It certainly has changed for the field of aging. There is no question about that. Aging research is now strongly rooted in the scientific main stream, and there are a number of interesting reasons why the field has become acceptable. It is part of main stream biology today, partly initiated by the changing demographics of populations in developed countries. We now have an increasingly greater proportion of our population who are elderly, and that is a very potent political and economic force. And potent economic and political forces ultimately meet with science, as they did in this case, and promoted the field. The most important event in the US was the establishment of the National Institute on Aging, in which I had some direct role, and indeed was offered the first directorship. As a matter of fact I did not accept it for two reasons. First, the salary was too low to support a university education for my five children, and second, I asked the NIH to send an attorney to my lab so that I could talk to him about the ownership of my WI-38 cell strain, which was an unique question then in not only science but also in law. Who owns the rights to a self-duplicating system? At that time the patent office refused to patent WI-38 cells because living things were unpatentable in 1962. So, I lost the opportunity to patent WI-38 cells which are now used to manufacture products that reap in the mul-

tiples of billions of dollars annually for many of the world's pharmaceutical companies. I have gotten only two good dinners. This could not happen today because living things like WI-38 can be patented. But in 1975, when the NIH sent to me an accountant, and not a lawyer, this person concluded that I had stolen WI-38, which triggered the lawsuit that I described earlier.

The Hayflick phenomenon and cancer

SR: Most of the experimental gerontology research that has given scientific credibility to aging research is based on the Hayflick system and the Hayflick phenomenon. How do you feel about naming this whole phenomenon of cellular aging in vitro as the Hayflick phenomenon?

LH: I am happy that the observation has finally been almost universally accepted. It was Sir Macfarlane Burnett, Nobel Laureate from Australia, who coined the phrase 'Hayflick Limit' for the first time. He was writing a book on aging, and was aware of my work, and he coined that phrase. I have never used the phrase and have always called it the Phase III phenomenon as stated in my original paper. It is a mixed blessing. I am not a seeker of self-aggrandizement, but if my colleagues choose to use that term, fine, I have no objection to that, but I don't encourage it.

SR: What has this phenomenon taught us about the basic aging process?

LH: I don't think that it is fully appreciated that our demonstration that normal cells are mortal provided the essential information that made the concept of 'immortalization' possible. One of the major areas of interest in cancer biology and now in aging research is the change from a mortal cell population to an immortal cell population. That was the key part of our original paper, because you cannot talk about immortalization of cells unless there is such a thing as a mortal cell. Since much of cancer biology today is based on an understanding how a mortal cell becomes an immortal cell, that was the main thrust of our original paper. As to what this has taught us about aging research, it is this. The finite replicative capacity of normal cells, now known to be governed by telomere shortening, is probably telling us more about longevity determination than it is about aging. The hundreds of published physiological decrements that herald the approach of Phase III is the aging process because aging is simply an increase in unrepaired molecular disorder.

SR: Yet it took cancer researchers more than 30 years to realize that!

LH: Absolutely! So our contribution to this fundamental aspect of modern cancer biology is at least as important, if not more important, than the aging interpretation. If we had not pointed out that normal cells are mortal, then immortality would have been assumed to be the property of not only cancer cells but of normal cells too as it had been for the first 60 years of the twentieth century. My thinking about aging has evolved, and some of my positions about aging have changed 180 degrees because of new data. When I first entered the field of aging, it was in the stone age. So my views had to change, and I am sure they will change again. In our experiments we showed that normal mortal cells do exist and that there is a counting mechanism. We also showed that the replicometer was located in the nucleus. That is not well known today. My then doctoral student Woodring Wright and I demonstrated that the replicometer was located in the nucleus. I coined the term replicometer because it is really not a clock. A clock measures the passage of time. Telomere shortening is telling us about the number of rounds of DNA replication. A meter is an event counter, so I am calling this a replicometer. I never thought I would live long enough to see a molecular biological explanation of my finding. Today we have it, or we have a substantial part of it. It is telomere shortening. So, the past ten years of research on telomeres and telomere shortening have just been very satisfying for me.

Aging *in vivo*

SR: But all these explanations are for the ultimate phenotype of replicative senescence in vitro, *whereas in the body, as it has been argued repeatedly, this phenotype may never be attained for most of the dividing cell types. However, most of the current research is focused on this final phenotype, but what about these 50 or so doublings that normal cells have to undergo before they stop dividing? After all, the process of aging is the whole lifespan curve of cells in culture*

and not merely the end stage. There is progressive accumulation of damage that finally is a kind of signal for cell cycle regulators to become active. How do you think the Hayflick system can be utilized experimentally to understand how and why damage accumulates in mortal cell populations but not in immortal cell populations?

LH: In the years since the publication of our original paper there have been hundreds, if not thousands of publications showing an equivalent number of incremental and decrimental changes in the biology of normal human cells as they get closer and closer to Phase III. Assuming that those changes are going on *in vivo*, and there are data for that happening, then those changes, I would argue, are aging changes. Those changes which precede the loss of replicative capacity in fact fit perfectly the definition of aging, namely increase in molecular disorder. If that happens *in vivo*, then you have an absolute counterpart *in vitro*. People fail to appreciate the likelihood that the decrements that occur in dividing cell populations as they approach Phase III *in vivo* could have profound effects on non-dividing cell populations. Telomere loss, on the other hand, is telling us more about longevity determination than it is about aging. We do not know enough yet about the telomere system to argue against the possibility that as telomeres shorten they trigger losses in physiological capacity. What we know today is that telomere length is a measurement of permissible rounds of DNA replication and hence a longevity determinator of a dividing cell's capacity to replicate. I see this as a phenomenon distinct from aging. This distinction is not well understood in the biogerontological community. People talk glibly about aging genes when those genes govern longevity determination and not aging. I don't think there are genes that govern aging processes.

SR: Perhaps one can use a buzz word such as 'gerontogenes' to draw attention to the fact that when one is talking about any genes in relation to the progress of aging, without actually meaning that there are real aging genes. They are there only virtually!

LH: Longevity assurance genes, for example, or some other name. Yes, we need some better terms.

The aim of biogerontology

SR: Until now we have described the phenomenon of aging in many systems, and we still keep on describing it. However, almost all research grant applications are written containing a statement 'the aim of aging research is to improve the quality of life'. But one rarely sees any proper scientific experiments being performed to fulfill this aim. How do we go about intervening in the aging process to achieve better quality of life in old age?

LH: I am worried about a more fundamental question that is behind the one you asked, and that is why do it? What is the advantage for humans to have the power to manipulate the aging process or longevity determination? Why is that a desirable goal? The answer to that question is not clear to me. It is not necessarily good news today, for example, to have a pill taken each morning that would either arrest the aging process or permit us to live X number of years longer. Let us pursue that magic pill, because that is behind your question. Let us assume that we have now arrived at an understanding of the basic longevity determining processes to the extent that we have a therapy. The probability, first of all, is that that therapy is going to be available first to the rich and powerful. I am not sure at all that I would prefer to see the rich and powerful have a greater capacity for longevity than those who are not rich and powerful. I am worried also that tyrants, serial killers and other socially undesirable characters would have equal access to greater longevity. Of course, there is an opposite argument that all the good people and contributors to our civilization will also have the same fate instead of simply dying at an earlier age.

But it becomes an even trickier question. People who want to live longer are arguing from a base of perceived life satisfaction. That is, they assess themselves to be happy at a particular moment in time. Significant numbers of happy people are a very recent phenomenon. Life satisfaction occurs less in poorer countries and in relatively greater numbers in developed countries. People will be faced with this problem: when in your life do you want your aging process to be either arrested totally or slowed down. That will vary from person to person depending on their life satisfaction at the particular time when this opportunity presents itself. The probability is that many people who are sufficiently knowledgeable will realize that there are many people in their seventies or

later who will tell you that this is the happiest time of their lives. Their kids are married, they have no family responsibilities, they have bought themselves caravans, or recreational vehicles, and follow the sun from Florida in winter to Canada in summer and the reverse twice a year. This is the happiest time of their life; they are not wealthy but they have enough money to live comfortably. Had they decided to arrest their aging process at the age of 30, 40 or 50, they would have either delayed or eliminated the likelihood of experiencing the best time of their lives. So the decision to arrest the aging process or to prolong it is a very serious question. Not only that; not everyone will take this pill. I might choose to take the pill, but my kids might not, which means that my kids are going to become older than me! Human's ability to tamper with the aging process will produce societal dislocations and effects on human institutions that will be monumental.

SR: Of course that is a very important issue about longevity. But what about this question of healthy old age or disease-free old age?

LH: That is a completely different issue. There is no argument that there is a need to understand the etiology of the leading causes of death in order to intervene. But the resolution of diseases causing death in old age is not aging research. It is geriatric medicine. The failure to appreciate this critical distinction is a fundamental problem in the field of biogerontology.

SR: So, how do we go about it?

LH: That represents an area in biology that I think suffers from a fundamental loss in appreciating the role of biogerontology. For example, cancer, cardiovascular disease and stroke are more likely to occur in older cells than in younger cells. The question not asked, and that I think needs to be asked is: Why are old cells more vulnerable to pathology than are younger cells? I think that is the job of the biogerontologist. We wrongly assume that aging is a disease. It is not for several important reasons. Age changes simply increase the vulnerability to diseases. We are also not addressing another important question that was first raised by George Sacher. His perspective was that the key question in aging is not why we age, but why do we live as long as we do. That is a very important insight.

SR: What are the experimental approaches for that?

LH: There are dozens and dozens of approaches, but we must understand the nature of the problem. The nature of the problem is that age changes are stochastic, that is increasing disorder occurs at every level – from the molecular to the whole organ. So you cannot exclude any biological discipline as a potential contributor to our understanding of longevity determination and the aging process.

The future

SR: In your view, what are the hot areas in aging research these days?

LH: Well, there are hot areas of emphasis today but that doesn't imply importance. Calorie restriction research and antioxidant and free radical research are popular now. But many other areas have been neglected, too. First of all I am not sure that aging is reversible or manipulatable. I think what is manipulatable is longevity determination. My reasons for that belief are based on the indisputable fact that everything in this universe ages. Automobiles are a good general analogy. When you buy a Mercedes or a Ford, you have an innate expectation of its longevity. In the former case you expect it to live for 8–10 years and in the other 3 or 4 years. Why? Because the design and the construction material used differ in quality, in efficiency and in many other attributes. That is a perfect analogy with biological material. Also, there is no part of the blueprint for an automobile that dictates the aging process. I don't think, for the same reason, that there is in the genetic blueprint a gene for aging. Longevity can be engineered into an automobile and into an animal, but not aging. Disorder from order is the universal aging process. One can delay the appearance of the aging process only by tampering with the process of longevity determination.

The boardroom was suddenly getting crowded with people bringing in their lunches. The BSRA meeting had reached its lunch-break stage. We were also reminded of the lecture yet to be given by Dr. Hayflick immediately after lunch, followed by his interview with the BBC. So, finally I wanted to know:

SR: How would you like to be remembered – as a breakthrough scientist, a rebel, a thinker?

LH: Just a fellow who did his job, I suppose, that's all!! My job is to challenge authority. My career has been that of a rebel, and the things that I rebelled against turned out to be accepted, ultimately, by most scientists and most of society. So I guess I am guilty of being the arch typical iconoclast.

And so we left the room with Len Hayflick's humble words describing himself as 'just a fellow who did his job' engraved in my mind. And what a job he did!!