Sir Henry Harris

Personal Details

Name	Henry Harris
Dates	1925
Place of Birth	Russia
Main work places	Oxford
Principal field of work	Cancer genetics
Short biography	See below

Interview

Recorded interview made	Yes
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Personal Scientific Records

Significant Record set exists	Yes
Records catalogued	Yes
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Biography

Henry Harris was educated at Sydney Boys' High School, Australia, and at the Universities of Sydney and Oxford. After doctoral research with Howard Florey at the Sir William Dunn School of Pathology, Oxford, and a sabbatical year at NIH, he became head of the department of Cell Biology at the John Innes Institute. He succeeded Florey in the Oxford Chair of Pathology, later also becoming Regius Professor of Medicine. He remains active in research after retiring in 1992. A list of honours and prizes can be found in 'Who's Who'.

INTERVIEW WITH PROFESSOR SIR HENRY HARRIS, 7th JUNE, 2007

It's Thursday 7 June and I am talking to Professor Sir Henry Harris at the Sir William Dunn School of Pathology at Oxford.

PSH. Can I start a little bit at the beginning and just ask where you were born and brought up?

HH. I was born in a small town in Russia, from where my parents emigrated during the starvation year 1929 to go to Australia when I was a baby, and I was brought up in Australia. I have no memories that are real memories of Russia. I was too young. I have memories that have been put into my head by conversation with my parents, but the only memories that I have that I know to be real start with Sydney, Australia, at Bronte Beach where we lived. It was a very hard time initially because my parents didn't have English and had no money and 1929 led into 1930 and that led into depression. It probably doesn't interest you much, but my father was an inventive man and he managed to get things to go in a small business during the depression and that more or less set us up in a lower middle class way. So I was educated first at, let's see, Auburn public school and then Kensington public school and then Bondi public school from where I went to a highly selective Sydney Boy's High School. The Sydney Boy's High School was at the top of the state school system. It was also part of a grouping known as the great public schools, which are a lot like English public schools and all the bright boys in this city competed, so it was very, very selective, very competitive, very academic and that was where I was educated and then won a university bursary and public exhibition to the university of Sydney, where I first read modern languages and then medicine.

When I was reading modern languages I didn't know whether I was going to do medicine or something else, but I became interested in doctor writers, either doctors who turned out to be great writers, like Chekov, or dozens and dozens of others, or whose fathers had been doctors. And I rather thought I saw at that time a rather astringent view of life that these medically trained people had and I attributed that view of life to the medicine. And I actually, this sounds terribly romantic, but is actually true I think. I actually entered medicine in order to become a latter day Chekov. I thought if I took a medical degree I could do some decent writing. And then half way through the medical course I read a rather interesting neurophysiology book, Fulton's disease of the nervous system, and I got hooked. I started doing experiments while I was still an undergraduate. I think I published a paper together with a friend while I was an undergraduate and as soon as I had done my compulsory year in medical registration at the Royal Prince Alfred Hospital in Sydney, I went back into the laboratory and stayed there for the rest of my life, but kept writing short stories. That's about it.

PSH. Can I ask, was there anybody prior to yourself in the family who was medical or scientific in any way?

HH. Nobody. There was nobody in my family, prior to myself, actually went to university. After me there were cousins that also went to university. They were younger than I was. I think I was probably the first. My father read

books all the time and he knew what learning was about but we had no scientific background, no learned background as it would be understood now, in the family.

PSH. Do you think in terms of factors making you come into medicine, apart from the literature, do you think there was any other clear factor which took you towards science and medicine, or was it just the interest of it.

HH. Well, there was a theory at the time that positive and negative after-images, visual after-images, were all due to effects taking place at the retina and I thought well, why only the retina. It could be the lateral geniculate body or visual cortex or what not, and I thought I should be able to sort this out if we put electrodes in the right place and shine lights into cats' eyes, we would be able to find something out. Well there was some equipment that Eccles, Katz and Kuffler [Stephen] who had worked at the Kanematsu Institute at Sydney Hospital, had left and ended up in the University and there was a bloke who thought he could use it. I asked him whether I could have a go at this experiment and so we got a cat, and we anaesthetised it as I can remember. The first, really, we got from what we thought was the optical cortex was a biphasic wave going boomp boomp boomp. We'd got an electrocardiograph from the optic nerve! It turned out this fellow thought he knew how to use the equipment, didn't know how to use it and I was mucking about with it, when Archie MacIntyre, who was a good neurophysiologist, I think he became Professor in Adelaide and stayed there for many years, blew through the place and he asked me, he was told there was a crazy kid down there mucking about. And he asked me why we chose the cat for these things and shone various coloured lights, green lights, red lights into the cat's eyes. I said physiologists always work on cats. He said yes, but cats are almost colour blind. Anyhow that piece of information finished my career as a neurophysiologist.

That was my first thinking, then I read somewhere that you might be able to do something with acute nephritis - they thought it was an immune disease - by blocking the antibodies, and the paper we published was 'Blocking of antibodies in vivo'. That was even more farcical and the paper was a disgrace, but the Professor of Medicine there was so delighted to have anybody publish anything from his department that he let it go. It saw light of day but it's absolute bunkum. But anyway I quite liked the quiet of laboratories and I quite liked seeing a problem and having a go at it, and I quite liked the company that seemed to be there. In Sydney people with a medical degree went to the University if there was something wrong with their lungs or they couldn't make it in practice and so on but they were a gentle crew. By the time I was doing my rounds in the hospital as a Junior Resident Medical Officer, oh a little earlier, I had won a prize called the H E Waldron memorial prize in bacteriology. It was a special prize because the Professor of Bacteriology actually worked in the Dunn school years ago, Hugh Ward, and he always used to set a question which you needn't answer if you didn't think you were in for the prize, and it was always an experimental sort of a question, and I remember the question in bacteriology, when I sat the paper was "How would you design an experiment to determine the therapeutic efficacy of vaccination for whooping cough?" which, when I think about it now, is a tall order anyway. So I wrote something that wasn't totally disgraceful. I

won the prize and while I was on the ward in the hospital, I got a telephone call from Hugh Ward, the Professor of Bacteriology, to say that he had Florey in his office and would I like to meet him. I said I must be dreaming. You mean *the* Florey. He said "Yes. Come on over". So I dropped what I was doing, and I went over and there was Florey. He looked very much like a moderately successful business man, but his speech was very laconic, very direct and he said "Ward tells me that you like doing experiments Harris, is that right?". I said "Yes, I quite enjoy myself, break a bit of glassware, make a noise". He said "Well how would you like to come to Oxford?" I said "Well It's like asking a man in the desert whether he would like a drink." And he said, we'll see what we can do. In the interim I received a visit from 'Panzy' Wright, who was the professor of Physiology in Melbourne. 'Panzy' is short for chimpanzee, not for sexual orientation as they call it, because he was a very hirsute man, and he offered me a job in the Department of Physiology in Melbourne and I'd not heard anything from Florey. I'm not quite sure of the precise temporal order but it was something like what I'm saying, and this was a job in the Physiology Department in Melbourne and I agreed to take it but I told Panzy that I'd had this interview with Florey, you know, probably end up, after I'd spent a little time in Panzy's lab, going to Florey if he could arrange it. So I decided it was time to get married. I had £60. Forty of it went on the honeymoon. So I arrived in Melbourne. There was a housing shortage but I managed to find a place which we would share with a very nice man called McConnen who owned a little house but he wanted a month's rent in advance. I didn't have it, so Panzy wrote out a cheque for a month's rent in advance and that got me going. I paid him off gradually. Then after I had been there for a while, there were all sorts of other schemes that came up that Panzy was involved in. He spent his life really building up businesses in Melbourne. But then I was awarded via Florey, an Australian National University travelling scholarship to come to Oxford to read a DPhil under Florey, which I did. That was in April 1952, and I've been there ever since.

PSH. May I ask, your actual PhD, what was it on?

HH. Chemotaxis

PSH. In any special . . . .

HH. The PhD. Florey, there was a fashion going then that was a stuff called leukotaxine which was supposed to have some marvellous properties. Anyhow Florey, influenced by the success of penicillin, thought that if there was anything in this it would be interesting to purify it and see what it did and so on. So I devised a new technique for measuring chemotaxis.. You no doubt have seen these pictures of 5th Avenue or Times Square in New York with the headlights making traces by leaving the shutter open. So I devised a technique for doing this with leucocytes, so I could record their traces everywhere they'd been and got very nice chemotaxis tracings and I had a look at polymorphs and macrophages and lymphocytes, and that was my thesis.

PSH. What took you then, moving on a bit, towards the more genetic orientated, the more cell biology orientated path?

HH. I actually had a celebrated row with Florey about that. I wanted to get away from cells that didn't multiply. These cells walked around the place and they walked in various directions and so on, but I couldn't get terribly excited about that and I knew that if I was to make any real biological sense of it, I had to devise a whole new methodology. We couldn't even separate the proteins properly at that time and I didn't want to proceed with the chemotaxis. I said, I would like to have a look at some cells that are multiplying and see what they do. So Florey was a very dominant character. People under him did as they were told and perhaps because of my background or my temperament, I was not an easy man to induce to do as I was told, so Florey wouldn't see me for a week. Eventually I went to see his secretary and said, if I am to go I would like to know, and at this point his secretary, a very bright lady, arranged for me to see Florey and he met me stern faced, and I said I would like to have a look at fibroblasts. Nobody can grow them except in great lumps and I'd like to get some quantity into this and see what I can do with it. I do remember during this exchange saying that that's what I'm going to do and all you can decide is whether I am going to do it here or somewhere else. And Florey said "Harris you need a holiday. Go and take a holiday". He was a much bigger man than I was and I said OK, so I went and took a holiday and when I came back he said OK, go ahead with what you want to do, but remember you are on your own. So I went, as you will see from the publication list, I worked out good quantitative methods for handling fibroblasts, and then I was deflected in an interesting way.

Jacques Monod, who was a great generaliser and a very uncompromising individual, very Cartesian view of the world, he said there was no such thing as protein turnover. I had been brought up on Rudolph Schönheimer's book, The Kinetic State of. Body Constituents. He said this is all due to cells dying, that the cell proteins are completely stable. Because in exponentially growing bacterial cultures it looked as if they were. I didn't like that much because I thought in the liver and the kidney, there can't be cells dying at the rate that could possibly account for the protein turnover that people were measuring. So one of the cells that I'd been working with was the macrophage. Macrophages stay alive for 3 weeks if you look after them and they don't die, they go about their business, and my first DPhil student that Florey let me have was an organic chemist. We synthesised reagents of various sorts and we showed that in this cell without any cell death, there was a massive turnover of protein, so Schönheimer was right and Monod was wrong.

And I thought while I'm about it I will have a look at RNA because of Siminovich and Graham. Siminovitch who worked with Monod had published a paper that all the RNA was stable. I said well, let's see if it's like the protein story, and there I found a massive turnover of RNA in the macrophages. So I said, let's see if this is also true of multiplying cells so I then moved into the fibroblasts, and there we found a massive turnover of RNA and I wanted to know where it was taking place, so sent it off for auto-radiography and we found it was taking place in the nucleus. Now at that time the messenger RNA story broke, that the RNA that you labelled very quickly was the message that went across. We couldn't get it across to the cytoplasm. Of course radioactivity did accumulate, but at a completely different rate which was in no way connected with the rate of breakdown, and then we analysed isolated nuclei. We came to the conclusion that the rapid turnover was taking

place within the nucleus, and that produced a very interesting – I'm coming to your point in a minute! – that produced a very interesting change in my life, because the data was not believed and I was relegated to the lunatic fringe, and Florey called me in at one stage and said "Do you know what you are doing?" and I said "Yes". "How long do you think it will take them to believe you?" I said, "no idea", "Oh about 10 years", that was about right. But what happened was that eventually we ground them down and we forced them to admit that there was a massive turnover of RNA within the nucleus, and that the smear of radioactivity that Sydney Brenner and Jacob were talking about was not the message. It was the non-message. It was the stuff I was working with that turned over RNA. Darnell and various other people eventually agreed that there was a massive turnover of RNA within the nucleus in and one didn't begin to make sense of that until introns and exons were found. At that time, this was before Fred Sanger could sequence nucleic acids, and I did a lot of kinetic studies which showed the enzyme involved, very nice balance sheet studies on the RNA but I was determined at that time that we wouldn't really know what this was about, we could do a lot of shadow boxing but we wouldn't know what it was about until we could sequence some of this stuff so that we could find out what it actually was. Well it took 10, 15, 13 years I think but a number of years after that that sequencing became a possibility, and then about 13 years later they found the introns and exons and it became quite clear that not all but most of the RNA made the nucleus made on the introns was not coding any proteins and I actually said this in an article, which is the thing, actually published as a book. It's called "An RNA Heresy in the Fifties". That was an article which had been reprinted in a book called *the Inside Story*.

PSH. I know it from Trends in Biochemical Sciences Papers

HH. That's right.

PSH. Jan Witkowski.

HH. That's right yes. Well I have an article there which says precisely that, that the RNA which was turning over rapidly, was the RNA that was made on non coding DNA and had a completely different function. So in a curious way that was prophetic. Now it's not a good thing for a young man to be relegated to the lunatic fringe but it's very good for your moral fibre. But I was working on this RNA problem and gradually grinding this information into the system here, but there was no job here, no vacancy, and the idea that we would be going back to the Australian National University when Florey went back to be the Director, collapsed, for a lot of unpleasant reasons. But if he wasn't going to go back, I wasn't going back either. And then, I think Hans Krebs, I'm sure about Peter Medawar but I think Hans Krebs, and Peter Medawar, were on the Agricultural Research Council at the John Innes. They were putting up a new laboratory of cell biology and they were looking for somebody who posed as a cell biologist and Peter Medawar threw my name in the hat. I knew him a little from contacts with the Dunn school, and Krebs also, and I was offered this job and I went down to have a look at the job. It was at Bayfordbury at the time. There was this beautiful new lab, wonderful parkland and I was just there to do what the hell I liked. So I took the job. Some eyebrows were raised, including Florey's, because people with medical degrees don't

generally go to botanical institutes. But it left me with one interesting residue. I can now tell a carrot from a turnip, which I couldn't earlier on. But when I went to the John Innes, there was a man called John Fincham, and he was working with Neurospora, complementation of the glutamic dehydrogenase locus, and this takes place in Neurospora and other fungi by hyphal fusion, and this was next door and I thought this would be wonderful if we could get our cells, animal cells, human cells to fuse together in this way. And then I had, what I think still is an interesting thought. It was the era of the uniqueness of the individual, Medawar's doctrine, how these terribly specific things, that you couldn't transplant A to B without the proper receptors but I thought, in Neurospora, if you get the wrong hyphal fusion, the thing collapses because evolution hasn't worked on that system. It's a regular mating system, so that if it's a good cross it will go, if it's a bad cross the thing collapses, but I thought all of these determinants of specificity, in animal cells they are all on the surface, but if you get underneath, all these tissue culture cells are alike as two peas. Mouse cells or rat cells, you have to be told what species it is and I thought, if I could get under the skin they would accept each other, but I didn't do anything about it, it was just a thought I had. And then I went to the library one day and took down an issue of Experimental Cell Research, and there was a paper from Japan by Okada in which he was studying fusion induced by a virus that he called HVJ, haemolytic virus of Japan. He was interested in the fusion process, what it did to the membranes and so on, and remained interested in that until he stopped doing work. It was fusion that interested him. What interested me was that you could use the virus to induce animal cells to fuse and furthermore you could do it even if you inactivated the nucleic acid of the virus. He was able to show that. So I thought that would be the way to do it. Now I could have got in touch with Elio Pereira who ran the virological collection in Mill Hill. It is only forty minutes away from Bayfordbury, but I didn't, mainly because I was not a virologist. I didn't grow things up in eggs. I didn't know virological techniques. And then Florey retired prematurely to become the provost of Queens, so this chair became vacant and either the electors mistook me for a much more distinguished Harris because there were many, many Harris's, or somebody leaned on the system. But anyhow they appointed me to succeed Florey here. I was in my mid thirties at that time and in Oxford that was pretty unusual, because it is a pretty conservative place. You have to sweat it out to get one of those chairs. And as a matter of fact, next door in the Botany Department, I won't mention his name, one very distinguished botanist said "who is this obscure botanist they have appointed to succeed Florey?"

PSH. Was that Cyril Darlington?

HH. Yes of course! Anyhow, when I came here, there had been a new appointment in the Department, John Watkins, who was a virologist and he had all the virological techniques and egg techniques so within a few weeks of my taking up the job, I called John in and said: "Look John, you know these viruses sometimes cause cells to fuse together", and in fact there is a long history of virus induced cell fusion making multinucleate karyocytes, a long history. And I would like to get that virus in, inactivate it and see whether I can fuse together cells from two different species. Why would I want to do that? To make a noise. I thought, we don't have any decent markers to work with in our multiplying cells in vitro. Differentiation markers are very difficult

although if we had species differences there would be no difficulty. We would have a plenitude of markers for chromosomal mapping, and I said I think it might work. Anyhow it's not a big experiment if we can get the virus, we can see what happens. So he wrote to Pereira and Pereira said he didn't have what was known as HVJ but he had Sendai virus which he thought was the same thing. So we got some Sendai virus in and inactivated it with ultraviolet light. They don't use this now but we inactivated it and I had going some HELA cultures of all sorts, and animals bearing Ehrlich ascites tumours, so I fused HELA and Ehrlich cells together. Well I didn't do it, John did the experiment. I gave him the cell lines and he fused them together and the next day he brought up some slides and preparations which clearly showed multinucleated cells containing both human and murine nuclei. Fortunately they are easily distinguishable morphologically by looking. So I thought, that's wonderful. If we have a heterokaryotic state which is stable, there's a lot we can do long before we do any genetics. We can see whether, for example, whether the control of DNA synthesis is possible, whether if we put in an inert nucleus like the red cell nucleus of a bird, would they reactivate it and so on. So I dived straight into the system and did all these things. There were a lot of discoveries came out very quickly out of the heterokaryotic system; a), that the regulation of DNA synthesis was done by positive controls not negative controls and if the cell made it, it would turn on the one that was turned off, never the other way. Then we did RNA, it was always the same, it turned on. That was the beginning of transcription factors of course, positively controlled. That annoyed Jacques Monod immensely, because he wanted everything to be [unclear] by repressors. Well there are a couple of cases of repressors but they are jolly rare and they don't represent a general system. But anyway, when we'd done this, John found in the literature, a reference to papers by Barski and Ephrussi and they had found a phenomenon which they thought was the formation of hybrid cells spontaneously in mixed cultures. They had only worked with mouse cells. The idea of crossing species never crossed anybody's mind at that time, but he had markers on different chromosomes and they were very confident that they did have hybrids, but many people didn't believe them. They thought there might have been artifacts from chromosome preparations, one overlaying the other. But the original paper was by Barski, Sorieul and Cornefert and I received an astonishing letter from Sorieul which contained a slide on which there was nothing but dust and the letter simply said "this is what happens when you fuse cells together". So I thought there's something wrong with Sorieul and then there appeared a paper by Sorieul and Ephrussi in which Sorieul spelled it out how that discovery was made. Sorieul was the cytogeneticist who was working for Barski and it was he who first observed the appearance of these cells and this was recorded in the literature which is discussed in that book. And then Boris Ephrussi moved in and took Sorieul away from Barski and the papers were then Sorieul and Ephrussi, and then Sorieul disappears. What happened to Sorieul is that he had an attack of acute schizophrenia and killed himself. So he was the discoverer of this.

So Barski and Belehradek - again you will find it the history and that is about right I think. They thought that these hybrid cells were created by the transfer of a nucleus from one cell to another and they recorded cinematographically the transfer of this nucleus from one cell to another and that was all bunkum and Boris, when our paper appeared in Nature rang Peter Medawar to ask

whether Peter Medawar knew me and could persuade me to send him a copy of my paper as Nature was rather slow to get to the United States in those days. So Peter Medawar rang me up and I said 'sure'. So I then sent Boris our paper showing this, and told him that in the interim, Charles Ford, who was then in the lab, had actually looked at the chromosomes and found any number of hybrid man/mouse mitoses, so those cells were actually capable of multiplication, inter-species hybrids. Now Mary Weiss, reminiscing again, the reference is given there - Boris had to rush off to catch an aeroplane and as he left he shouted to Mary that she must put rat and mouse cells together, and she put rat and mouse cells together and found colonies of hybrid rat-mouse cells. Now John Littlefield made a big difference, because we had small clones of our hybrid cells with hybrid mitoses, but they were rapidly overgrown by the parental cells which grew much better. But John Littlefield introduced these different selectable markers and so anybody could put these selectable markers into the cells and get out whatever. That was a big advance and then Boris did that as well. But nobody but us did anything very dramatic with the heterokaryons except Siamon Gordon at the Rockefeller Institute, and he was very interested in macrophage physiology, so he started a line there and eventually came to be reader and professor at Oxford. But we found out very many, well at least half a dozen very important things. I mean the reactivation of the red cell nucleus, everybody thought the red cell nucleus described in the literature as a dead nucleus dead as a dodo, and we reactivated it and Peter Cook who was a D Phil student of mine showed that this wasn't any kind of spurious enlargement. He actually showed that the bird enzyme was made in the human cell and this meant that the hybrid system was able to talk to itself in a perfectly comprehensible language between the two species, so that was really quite exciting. And then Weiss and Howard Green, Mary Weiss had left Ephrussi then and went with Howard Green. Mary, she and Howard published the observation that in man-mouse hybrids or man-rodent hybrids there was selective elimination of the human sets, that odd human chromosomes were retained and this enabled you to map in a very primitive way. Synteny it was called. So that started a great wave of activity. Walter Bodmer here, his people were mapping human chromosomes by this technique.

But compared to what you could do with real genetics, it was pretty primitive stuff. You'd got a marker and you'd got a chromosome and sometimes an added translocation, and I thought it should be possible to do better than that and the idea I had came again from the John Innes. A man called John McLeish who worked at the John Innes. He also incidentally committed suicide. I don't know whether this theme [??]....., but he was studying the effect of X rays on chromosome breaks so he was able to show the more radiation you gave the more breaks you had, and this was done on plant material because a plant chromosome was much bigger. And it occurred to me that for a given dose of radiation the chances of a break separating two markers would be much greater if they were far apart than if they were close together. So that from this we should be able to get order and distance, and I then got another DPhil student whose name was Stephen Goss, who remains the brightest DPhil student I have ever had. My contribution was nugatory. I simply said 'Look, this is an idea in my bonnet from John McLeish's work, and it may be quite impossible to do this with 40 odd chromosomes of a rather small size. But it's worth a go and so you can take your human set, you can

irradiate it and capture it'. And Stephen Goss did the lot himself. I used to come in every day, well not every day but pretty often. 'How you going?' He is a natural mathematician and I think at one stage he actually at my suggestion - I thought he had better go up and see the statisticians before he got too deep in this business and he had disagreement with the statisticians. He turned out to be right and the statisticians wrong. But he was an exceptional person.

And he wrote a thesis, the only case within my experience where the thesis work actually forms part of a genuine contribution which is in the text books too. They refer to the Goss-Harris, it's really the Goss technique. It was MacLeish's idea and I was part of it, but he did it all and that was an important thing, because that paper - and curiously enough this has recently been acknowledged by Terry Rabbits in Cambridge in a review he was writing - all the techniques where you randomly irradiate or randomly make clones, I mean the sort of thing the gene mapping business, not by Sanger sequencing, but by breaking the whole thing up, is all based on that. It is all essentially based on the fact that genes will - that paper, Stephen's and mine, really I would think it is not an immodest thing to say but that is the germ of the beginning of all shotgun techniques, because that was a shotgun technique, information shot. Of course this was done when computers were just burgeoning, because it would have been done by simple mathematics. You were going to ask something?

PSH. I was just going to ask, at what point was it that Charles Ford had moved over to here from Harwell?

HH. Well I can't give you the exact date, although they will have it in the file.

PSH. I was thinking in relation to the cell fusion work and the related work.

HH. Well, he was here when we did the cell fusion. I'm not sure whether he was here when we first began. It must have been very early because, he must have been here close to when we began, because in our initial Nature paper we say that we did see some hybrid mitoses and then in the definitive paper in the Journal of Cell Science, Volume 1, page 1, the beginning of that Journal, Ford is a co-author so he was involved in that.

PSH. Because I was just thinking, microscopically, rodent chromosomes are quite tricky to distinguish from each other aren't they?

HH. Especially a mouse set, is very difficult.

PSH. So I wondered if he had been a great help in confirming that the various hybrids you were producing were indeed hybrids

HH. No he didn't confirm anything. He established that this was the case. It was Ted Evans. Ted and Charles Ford worked together and the actual work, the hand work was always done by Ted Evans and Ted did the experiments I think. It would have been unlike Charles to have done them himself but he might have. I don't know. But he came and said they are hybrid mitoses, there is no doubt whatever they are hybrid mitoses. They are lining up.

PSH. That must have been quite a reassurance.

HH. Sure.

PSH. Because from my reading of other people's work there was a lot of criticism of different things because people often couldn't identify either chromosomes or pieces of chromosomes belonging to a particular species.

HH. Well there wouldn't be any difficulty with a human rodent hybrid or a human mouse because a mouse was always telocentric and a human was metacentric. Another thing happened, which was very very lucky. Within a year or 18 months of our doing this, Caspersson and Lore Zech got the fluorescent business and discovered banding, and I actually wrote a paper together with Caspersson showing that in these hybrids, it was all perfectly sensible and we were not hallucinating and so on, and he identified every one of the chromosomes and the human chromosomes in sufficient numbers. That's the only paper I had published with Caspersson so I saw a lot of him at the time and also some of his colleagues like Nils Ringertz, people like that. So then what do we do? Well, there was a bit of stuff in the literature about malignancy being dominant and everybody wanted malignancy to be dominant as a phenotype. 'Inexorable', you know and all these adjectives they used to describe it. That didn't make any sense to me. I thought it very unlikely that it would be a dominant. And I had a visit, a sabbatical visitor called Jack Miller who was a cytogeneticist and I said to Jack, 'I don't believe this story. We had a highly malignant Ehrlich cell. We will do this experiment looking more carefully at the chromosomes, and we did the experiment and we found that yes, these hybrids when you crossed a malignant and a non-malignant cell did generate some tumours but the tumours had highly segregated chromosome sets. They had thrown out masses of chromosomes, so the experiment was completely uninformative, because you don't have the two genotypes to compare.

Now I didn't have at that time an inbred mouse colony here at the Dunn school or even nude mice but I knew that George Klein in Stockholm had all the mice and had tumours to go with them. So I wrote to George and said 'Look I would like to do this experiment a little more carefully. I think it's worth doing'. George was very sceptical and said, Boris Ephrussi has already said it's dominant. Anyhow he is a generous fellow and he said, alright I'll do this. So he sent us the various cell lines, the various tumour lines. We made the hybrids crossing them with fibroblasts, lymphocytes, whatever diploid cells we wanted and Jim Kent, the head technician here, would take them down by car to Heathrow and his technician picked them up at Arlanda airport. Victor [?] in Stockholm, they'd be in the animals the same day, and it turned out to be exactly the opposite to what everyone was saying. The malignancy was not a dominant. It was in simple Mendelian terms a recessive and I'm not talking about various complexities of gene regulation. But as a phenotype that is clearly recessive. It's immensely difficult to try to get people to believe that that was so, but eventually Cold Spring Harbor had a meeting on tumour suppressor genes and it was all accepted that a normal cell had genes which had the ability to suppress malignancy, and I think that's a good discovery, that the normal cell has genes that suppress the phenotype. And Boveri - in

later years I read the monograph - he actually says that malignancy is much more likely to lead to a loss of genetic material not the gain of new material.

PSH. That's interesting. I must go back to my copy of that.

HH. Yes. That's the Origin of Malignant Tumours. You have that?

PSH. I've got the English translation.

HH. By the widow.

PSH. By his wife yes.

HH. Well I'll let you into a secret. I have done a new translation and annotated it. It will come out as a supplement to J. Cell Sci but it is also being published as a monograph. The company of biologists at Cambridge wanted to do it as a monograph, so they are going to sell it as a monograph. Marcella's translation is not all that wonderful actually, I think. I don't own Marcella's translation but I borrowed it from the library and gave it back. But I was given a copy of the original German. No I wasn't given it. My attention was drawn to an original copy that was available and I got it through the agency of a good friend, and one August I thought I must really read this right through. So I read it right through. Such a stunning thing that I thought I had better translate it. I have also extensively annotated it in terms of what this all looks like to a modern eye, my modern eye. So that idea was actually made very clear and very definitively in a way by Boveri and it is well worth looking up.

PSH. That's fascinating.

HH. But in terms of - the world was awash with oncogenes at that time, everybody was saying as the virus goes into the cell it adds information but of course it doesn't. It adds information but the information that it adds, is to block tumour suppressors.

PSH. Had Knudson's two hit hypothesis surfaced by that stage.

HH. That came out a couple years after our suppression of malignancy paper. It is interesting. Perhaps I am maligning him. I always quote Knudson. I quote him everywhere, but he never quotes me. Whether that's right or not I don't know. Maybe he does, I just haven't seen it. But anyway the reason that that caused a ground swell which our work didn't was because he drew attention to a specific gene, but by that time sequencing had been involved. So once you point your finger at a particular gene, everybody rushed in very quickly. They got the gene out and sequenced it and so on, the mutations, and then everybody started defining a tumour suppressor gene as one which has loss of heterozygosity, until it became clear that loss of heterozygosity occurs on a massive scale and many of these things are just going for a ride. Anyway it was certainly not the case that I knew about Knudson's interest. In fact Knudson's paper was drawn to my attention by Walter Bodmer who sent it me, who took that Journal. I didn't take it. It was a Genetics Journal I think.

PSH. Science was it? Or was it PNAS?

HH. He also wrote a review. Anyhow, Walter sent me a copy of it, and that was the first time, and I was very pleased because everybody started talking about tumour suppressor genes. But, but, although our experiments were done 20 years ago and hundreds, I suppose, of tumour suppressor genes, as defined by loss of heterozygosity had been identified, what genes in the normal cells were responsible for the tremendously dramatic effect we were able to do, actually suppressing the growth of a wide range of tumours, we didn't know. Why? Much like the RNA position I had reached a stage where I'd taken the cytogenetics as far as I could take it. I had mapped the region which was principally responsible for suppression, in the mouse it was on chromosome 4. I even got a translocation which showed me which bit of mouse chromosome 4 was involved in the suppression, but what the actual genes were, that was unknown. But then in 2002 the mouse genome, the physical map of the mouse genome, appeared and that also, of course, included the region I was interested in, and so I decided to take the problem up again, 20 years after the observation was made. And I think we now do have the gene which does this massive suppression. I'm fairly confident we've got it right and we've actually got a paper in press, on that.

PSH. Well done.

HH. Throughout my life, I'd take a line and then I'm prevented from pushing it further because the methodology was just not available. I knew I was not going to invent sequencing, that's somebody else's job. I knew I wasn't going to do the sequencing of a human and a mouse genome. That was somebody else. I had to wait until there was an advance, then I could do it. So that's more or less the story.

PSH. It's very fascinating, very fascinating.

PSH. If I could just finish by asking you just a couple of things, which I have been asking everybody actually I have talked with, and the first is, is there one particular person who has been a special influence on your career and life that stands out above others?

HH. Well if you are interested in scientists, that would have to be Florey. I was a pretty conceited, fresh, not very likeable fellow I think, when I was young. My wife thought I was alright. But there was one moment that was certainly formative. When I had finished the chemotaxis work, the DPhil work, I wrote it up as a paper, and the first sentence of that paper, I've forgotten the exact words, was something like 'this was the first time that this method had been applied to this problem and therefore etc, etc' and Florey struck that sentence out. I didn't understand why, so I asked to see him and I said "you've struck this out and I don't understand why". He said "is it the case that this is the first time this method has been applied to this problem. I said "Well it must be, I invented the method." He said "Well, Harris, let other people say that".

PSH. That's a wise remark.

HH. That had never occurred to me. And that phrase had a formative effect on me. I don't boast so much. And also a certain tough attitude to experiments in the sense that, if you gave a lecture, Florey would sit in the front row when we gave our seminars and if we started to speculate, his eyes would glaze over and he was totally uninterested. You got up, stated what the problem was, you stated what methods you use, stated the results, then shut up, and you did it with modesty, you didn't wave your arms around and generally go on. He had a way with photographs which was very interesting. When I first showed him - I was sharing a room with George Mackaness, room 47 up the corridor - and Florey put his head round the door and Mackaness said "Harris has got something nice to show you." "What is it?" So I got out the photograph I had. He said "You want to reduce the magnification". When Jim Gowans first showed a graft versus host reaction with a population of lymphocytes he showed Florey the photograph and his words were - so Jim tells me - "that's not much of a photograph". So he was very deflationary, but at the same time while he was busy deflating us all, he would go to London and say I've got a bright boy. He's doing some marvellous things. Then I'd get an invitation to go and see somebody in London. So he'd go and praise you outside but to your face he'd always deflate. The idea that you'd ring up a newspaper and tell them you had made a breakthrough. You'd be out of a job the next day. It was just the ethos at that time. You either impressed people or you didn't impress people, but if you tried to impress people you were dead. There were many aspects of Florey and of Florey's life that had no effect on me, in fact a negative effect on me. I didn't try to ape him but that aspect of him, the honesty, the lack of froth, the lack of embroidery about what you are doing and the practicality, to keep your feet on the ground and see what you can actually pull off. So that would have to be the case I'm afraid, although as a man there were mixed emotions, but that's inevitable of course.

PSH. The last question I've been asking everybody is, is there one particular, either experiment or area of your work that you feel special affection for or identification with as being a contribution that you really made, that stands out from the others?

HH. Well, I suppose that would have to be the development of cell fusion, because that gave rise to so many different avenues. People sometimes ask me why didn't we do monoclonal antibodies here, with Jim Gowans' work with lymphocytes along the way. I mean Jim had these lymphocytes and he was concerned that he couldn't get them to multiply in vitro. But what happened there was, I was busy suppressing malignancy and doing things which I thought were pretty important, and Jim was busy cannulating the thoracic duct, but there was a young Australian called Dick Cotton came and spent a year with me here and he went back to Australia for a bit and then came over and spent another sabbatical with Cesar [Milstein] and he came over to see me here and said: Look, I'd like to use your technique to examine allelic exclusion, because this has been an immunological phenomenon, and so I gave him some virus, inactivated virus and he took it over and he set the system up in Cesar's lab to look at allelic exclusion. Cesar had the myelomas. We didn't have any myelomas then but Cesar was interested in mutations that occur in the myelomas at antibody sites and he had the

myelomas growing and Dick set up the system of hybridisation and then Dick then went back to Australia and his position as a post-doc was taken by George Köhler and Köhler took over Dick's system and did it with spleen cells and that was monoclonal antibodies. I don't think Cesar was himself very personally involved in that exercise. He was very much involved in the structure of antibodies. Of course it was all done in his lab. I regarded, people here regarded, the experiment with the spleen cells as one of the spin offs of cell fusion, but of course to the immunologists it was actually manna from heaven. They took it over and it became a massive world exercise, but from our point of view, if somebody had asked us 'why didn't you do this experiment?' we would have said 'well you know I'm not an immunologist. I'm doing something else'. But it was via Dick Cotton that went to Cambridge and it really was due to him in a way, and Cesar spoke to me about this and he was perfectly clear. This is a slight aside, but it has to do with so many things that came out of the cell fusion, but I think the one very big intellectual step, although people would not recognise it as either intellectual or much of a step, was the idea that cells from different species, or anything you want, across differentiation, across malignancy, across species - you could cross the species barrier and crossing the species barrier for mammals, I think that was a good experiment. I mean it's not the one that I thought was hardest to do, or the cleverest, it was a simple experiment. There were some others of which I am more proud if you're thinking of experimental prowess, but I think that was the best of them. It generated the most things I think. Is that an immodest thing to say?

PSH. Not at all, and I think it's very true. Well, thank you very much. I am going to stop the machine here because we've nearly run out of time. It's actually been a great privilege, so thank you.

HH. Not at all. I think it's been about right. One always sees things differently from other people but everything I have told you has been documented, and most of the literature has been pretty carefully worked out in that book and you can check most of the points.

End of recording.