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**Professor Henry Harris in interview with Sir Gordon Wolstenholme**
**Oxford, 6 June 1986**

GW Henry, from the record it seems that your very first intention was not to enter medicine but eventually you did, and when you did, you did it rather spectacularly, and, if I may say so, have had and I hope are enjoying a very unusual medical career, if you can describe it as medical, but would you like to tell me a little bit of how you entered at all into this field of work.

HH Well, it was in Australia, at Sydney University, and I matriculated when I was sixteen, and my father, who was not a formally well-educated man - he'd been deprived of education for a variety of reasons…

GW Was he a refugee?

HH The family came originally from a little country town in the Pale of Jewish Settlement in Czarist Russia and he came out in the famine times and then settled in Australia and tried to make a living in the heart of the depression, and did succeed in making a living although he was out of work for a while. My grandfather had actually come out to Australia long before that, and that was why my father had come out.

GW Your father followed your grandfather?

HH Yes, my grandfather had come out to Australia via China in an earlier time, so some of the family was already in Australia before my father came out. My memories start with Bronte Beach, Sydney, sweltering under an Australian summer sun. But my father, anyhow, he had a great respect for learning and thought it would be a good idea if, whatever I did finally become, I got some sort of a general education before I took up any kind of professional training. That was a view he had on life and as I'd won what was known as a public exhibition, which remitted all my university fees, it was all done…

GW That was a school sort of scholarship.

HH No, the state government gave, I think, one hundred open exhibitions, that is irrespective of family income, and I won one of these. And I was quite undecided what I was going to do. I decided quite late, and I'll come to that. So I came up first and I read modern languages. I read French and German, and we didn't take Italian at school and there was a crash course in the University to bring Italian up to university standard, so I read French, German and Italian, and sat in on a lot of philosophy and history and whatnot and just had a whale of a time – chased a lot of girls. And then, I don't think I ever thought that I would make a living out of modern languages, it was always a prelude to something else, and what that something else was going to be was quite unclear. Now the reason I entered medicine is so romantic you will have difficulty believing it, but I have some documentation which can actually support this view of my motives. While I was reading modern languages I became interested in doctor-writers. Chekhov, of course, he bowled me over and still does, and then I became interested in... I read [Arthur] Schnitzler. I thought a great deal more of Schnitzler then than I do now. I got hold of a… in a second hand bookshop, [Alfred] Döblin, *Berlin Alexanderplatz*, and other doctor-writers. And I formed the idea that maybe I could be a doctor-writer. I found something about these chaps, a slightly astringent, slightly cynical view of their environment which I liked, and I actually decided to read medicine in order to inform my writing. I was writing woolly stuff and it was published in odd magazines and so on. And that must have been a fairly genuine motivation for a bit, because in the first couple of years I only did enough work to avoid being thrown out, but I wrote a lot of non-medical stuff.

GW But had you done any biology or chemistry at school?

HH Well, in the New South Wales educational system there wasn't much choice. It wasn't as here that you specialised very early. And this came to my mind fairly recently when one of my children asked me for a book and I said, 'I think I have it as a school prize,' and I dug it up and it appears that in the year before leaving the school, although I was reading French and German and Latin and what not, I'd come top of the year in physics, so we were still taking... I mean, you took ten papers or eight papers.

GW This is very much like Continental Europe isn't it?

HH Yes. So when I entered the first year in medicine, physics and chemistry was a cakewalk. I had to lean a bit of organic chemistry, but I hadn't been so removed from that at school early that it was a great sweat getting it up. But I didn't actually become interested in medicine until about halfway along in the third year. By chance I got out of the library, not a set book, a book called the *Physiology of the Nervous System* by John Fulton,[1] which all the physiologists tell me is a dreadful book. That may well be, at least as far as its reliability is concerned, but it was written in a very different way from the others. It was written in a historical context and experiments discussed and future possibilities were adumbrated and I read that with great enthusiasm and caught fire and then started getting, as an undergraduate, seriously involved in some bits of medicine, and then I started coming top of exams in at least the things I was interested in. But up till that point, I almost thought at one stage I would give it up because it was all so dull and was taught so badly. So that's how it happened.

GW On the clinical side, did you get involved at all?

HH Well, yes, I got a medical degree and I did my statutory year in the hospital, which was required in order to get a registration, but as a medical student I found that clinicians – there are some notable exceptions; I mustn't be too severe, but on the whole

[1] Fulton, J F. (1939) Physiology of the Nervous System. London; New York: Oxford University Press.

– pompous and opinionated, and they had very strong views about all sorts of subjects they knew nothing about.

GW And which had never been checked?

HH Well they would talk about history, or politics and modern languages, or they'd misquote Latin tags, just to show off, and I found all this bleating rather insufferable, and I cut a lot of the clinical teaching, but I must have got enough by taking it in via the skin I suppose...

GW I'm trying to force a contrast between those days and being regius professor in Oxford, of course.

HH Yes, well, I mean I did pretty well at the examinations at the end. But it's largely luck and you always get a few things that you can shine on, but on the clinical side I think I must have been a disaster. But I quite liked my year in the hospital. I was at the Royal Prince Alfred Hospital and I thought it was going to awful, but in fact I quite enjoyed it, mainly because of camaraderie. There you get closeted with a group of people, I mean you lived together and you see them, day in day out, in hilarious and in harrowing situations and you form some quite… there are still some friendships that have survived the passage of the years. And I quite enjoyed it as a form of sport, you know, running around the wards and feeling important and getting involved in very comic situations, sometimes. So that was much better than I thought, and then Pansy Wright,[2] who was the professor of physiology in Melbourne, offered me a job and I went into the lab and I've stayed there ever since.

GW Yes. But very, very soon you got a... was it a national scholarship to Oxford?

HH Yes. What happened was, the only professor in the Sydney Medical School, I think, that had ever done a piece of work that is still remembered was a man called Hugh Ward, who was professor of bacteriology,[3] and he had been at the [Sir William] Dunn School [of Pathology], before [Howard] Florey's time – in fact he rowed in the Oxford eight – and then he went to Hans Zinsser at Harvard and became an associate professor. He was an interesting bacteriologist. And he made his gesture to science in the form of a special question that he set in the bacteriology paper, which was the only question that was ever set, in my experience in the medical school, that couldn't be answered simply by rote learning, everything else was just memorisation. But he always set this question which made you use your 'nut' a little, and on this question there was a monetary prize which to me was very important, and it turned out that I won that prize. And when I was a resident medical officer… in fact, I was doing a bit of anaesthetics and I was putting an old lady to sleep before going into the operating theatre, and I got a telephone call from Hugh Ward, from the Medical School, saying that he had Florey with him and Florey would quite like to speak to me. 'Florey, <u>the</u> Florey?' 'Yes, Florey.' So I managed to get out from under and tore across to the Medical School. And Ward must have drawn

[2] Roy Douglas Wright (1907-1990) Professor of Physiology, University of Melbourne (1939-71).
[3] Hugh Kingsley Ward (1887-?) Bosch Professor of Bacteriology, University of Sydney, 1935-52.

me to Florey's attention. Florey was then trailing through Australia looking for young people whom he might in the end recruit to the National University in Canberra where he was setting up the John Curtin School. And he asked me a few questions about what I knew and didn't know and then he simply said, 'Would you like to come to Oxford?' It was like asking a starving man whether he'd like a square meal and I said 'Well, sure,' and he said, 'All right, I'll fix that,' and it was all over in about ten minutes. Florey was very laconic, and I walked out into the bright sunshine and knew that I was going to get a scholarship to Oxford, and it happened. I did tell him that I'd already agreed to go to 'Pansy' Wright in Melbourne and he said, 'Well, that's all right, you can pick up a year's physiology and then and then come to Oxford,' which is what I did.

GW Which is what you did.

HH Then I came to Oxford and read my DPhil with Florey.

GW Before we move to Oxford, just one personal question: did your father live to see your succeed in this way?

HH Yes. Well, my father… my father was a little doubtful about the choice in the end. I mean, he thought medicine, fine, but then in those days taking up medical research was still financially a pretty precarious business, and I'd married and children came and I was living in a little semi-detached, or quasi semi-detached place, up in North Oxford in a very modest sort of way, just rubbing along. And my parents came over from Australia and visited us in that period. It was in the post-doctoral period; no job and on annual grants; no great certainty that there would be a job. And my father wondered then whether I was being sensible; whether it might not be better to come back to Australia and the affluent medical scene and the sunshine and so on, and make a financial killing as most doctors did out there – yes, most doctors, I suppose. He was a little uncertain, but, yes he lived to see me succeed Florey and my parents took a lot of pride in that.

GW Of course. When you came to Oxford you worked, as you say, for you DPhil with Florey. Within a year or two you became a sort of director of research with the British Empire Cancer [Campaign]. How did that arise?

HH Yes, well that's very funny. That's rather a grand title for what it was.

GW It sounds very grand for a man within four years of qualifying.

HH Well, I'll tell you exactly how it happened. I'd done my DPhil and… well, a whole lot of rather interesting things happened, but I won't go into them, but in the end Florey said would I stay on in the Dunn School, and I said 'Nothing better,' but I couldn't stay on the stipend that I was receiving , because I was receiving I think £600 a year from the Australian National University, of which something like 50 per cent went in rent, furnished digs and so on - £650 it was. Then Florey said, 'How much would you want?' and without thinking about it, off the top of my head, I said 'I'd want twice that amount.' 'Twice that amount he said.' And he rang up Sir Charles Dodds, who was then the

Chairman of the Scientific Committee of the Cancer Research Campaign and asked him, over the phone, whether he could provide £1300 a year for a slightly wild but perhaps promising young Australian, and Dodds just said 'yes' over the phone. It was in the days when you could do that. My only regret was that I hadn't asked for more, three times as much. But when the form came that was going to make it all right for the committees, there was a place called 'director of research' and I asked Florey whether he was or I was, and he said 'No, you're the director of research.' So I became the director of research and that is why the title 'director of research, British Empire Cancer Campaign' – that's formally correct, but that was really just annual grants. Perhaps they ought to take it out of the *Who's Who* or something.

GW But did that in any way affect the nature of the research you were doing?

HH No, no, the Cancer Research Campaign then, and still now, takes a very civilised view of what cancer research is, and if people are doing good fundamental cell biology, they would regard that as, by definition, relevant to their objects, and I'm sure that's right. In fact, later, when I succeeded Florey to the chair, they formed a unit around me, which was a cell biology unit, and that exists to the present day and they have supported me very generously all my life, working life on the understanding that I would be doing fundamental cell biology. I didn't actually turn my attention to something that was directly cancer until I thought the time was right to do it.

GW There was no pressure of course?

HH None whatever. I couldn't ask… I raise my hat to them there. They've been absolutely splendid.

GW You succeeded Florey, I think in 1963.

HH That's right, yes.

GW And then, of course, to everyone's surprise, including yours, were regius professor [of Medicine] in 1979.

HH Yes, well that…

GW I don't mean it offensively, but how did that come about?

HH The regius professorship. Well, I really can't give you any inside information. You know, of course, how regius professors, or some regius professorships certainly, the old Oxford ones, are made. The appointments secretary of the Cabinet Office – or the patronage secretary, as he then was – goes about and makes a lot of enquiries up and down the country, at Oxford and elsewhere. Now, in a fit of immense conceit I could imagine that my colleagues in South Parks Road, that is in the science area, might have put my name forward, but I think it unlikely that it would have got very far unless some of the clinicians at Oxford hadn't said that they thought it wasn't a bad idea. Now, it's not at all clear to me how that came about because I'd never been at all accommodating in my views about this great distinction between clinical research and non-clinical research. I mean, I think in my view there are only two kinds of research, good research and bad research, and whether it's done in a laboratory or in a field or a ward is utterly irrelevant, and clinical research simply has to be judged by the same criteria as any other kind of research: if it's no good, it's no good, and I never minced words about this. So I wouldn't be the sort of chap who would automatically come to the mind of a group of clinicians, but some of them in Oxford, or elsewhere, must have thought it was an interesting thing to do, and, in fact, Alex, my wife, and I were on a holiday in Crete having lunch on a sunny terrace and one of the waiters came across and said there was a telephone call for me from Oxford. I thought that was pretty ominous because the only person at Oxford who knew where I was my secretary, and she wouldn't ring me unless there was something terrible like a fire or something of this sort, and when I came to the phone she said, 'No fire, there are just two letters from 10 Downing Street, what should I do with them?' I said 'Open them.' There was one letter from the prime minister and one from the appointments secretary. The Prime Minister wanted to know whether I'd allow my name to go forward to the Queen for this position. So somebody, or some group of people must have thought that a chap with a straight scientific laboratory background had something to give to the scene.

GW The time was very right for such a view, but nevertheless it was surprising.

HH It is surprising, it is surprising and it created difficulties, because one thing that was not negotiable was that I would give up my experimental work. And over the years, a lot of things have been built up in the Dunn School to make that possible, that actually required quite a bit of University negotiation and soul-searching before a scheme was worked out that enabled me to stay on in the Dunn School and continue my work and do the duties of the regius professor, whatever they might be. But that's one of the wonderful things about Oxford: whatever the statutes say – and nobody's ever too sure what they do say – if you can carry your colleagues, you can do anything you like, if you can't, you can do absolutely nothing. I mean, it's a genuine democracy in that sense. So the thing was mulled over by the various Faculty Boards, and General Board, and Hebdominal [Council]… all the University bodies, and in the end a scheme was worked out, which, it's not for me to say whether it has worked well, but anyhow it made it possible for me to accept it and then I said, okay.

GW It obviously was a splendid move.

HH You might ask, I suppose, what I thought I might contribute as regius professor and I think there is little. In the clinical scene… I mean South Parks Road, the science scene, that's straightforward, but in the clinical scene there is always a tug of war between the people who want to introduce some science into the clinic and the good doctors. They are not mutually exclusive, but there are two points of view and on the whole in this country the good doctors have won out – on the whole. I think… and in any competition for funds or developments and so on, it is the service requirement that, on the whole, has won out. Now, in Oxford, the opportunities for doing something different are so spectacularly attractive that I thought I could do something. And there seemed to be a general desire that the scientific base of clinical medicine should be strengthened and developed in Oxford, and I like to think that I have contributed to this in a number of ways, which perhaps the most important is that I sit *ex officio* on all the electoral boards, even to the clinical chairs, and all the professors that have been appointed in the clinic in Oxford are chaps who know one end of an experiment from another, and that means – I mean I won't mention…– but it means that it is a very distinguished clinical school at present, in terms of the depth at which it operates.

GW Undoubtedly. Yes, if one had a child one would certainly hope that they might…

HH That seems to be the general view, the University Grants Committee's view and everybody else's view. It is not my doing, but I have contributed in certain ways and things come up from time to time and we induce some good professional scientists to enter the clinical area and find some jobs for them when the money… So I can't really assess to what extent my own intervention has been important here, or to what extent I am simply being carried along by what, in any case, is a view held by some very important people in the clinical school, but I haven't impeded that progress and so I think that's been..

GW Has any non medically qualified person being given a chair within the medical faculty.

HH Within the medical faculty?

GW Well, I meant…

HH In the clinical. Well, that is very difficult. If he has statutory duties in terms of looking after some patients, it would be very difficult to do that. I think it could happen in clinical biochemistry. It happens that our professor…

GW I mean there are a few places, especially in the States where this has happened.

HH Yes. Well, I think that it is altogether possible. I mean as I look… it requires some softening up of entrenched positions, but as I look… I mean Peter Medawar was a perfectly plausible director of the National Institute and [Charles] Harington before him. And it isn't necessarily the case that if you have a large department of medicine, or a large department of pathology, or clinical biochemistry… that the man who actually runs it could be anything. I mean… but if the terms of reference of the job require that it carries legal responsibility for certain things there is very little you can do. But again I take the same view about that as I do about experiment; I mean have a look at the job and then just get the best chap you can for it, and you know what sort of ticket he has is really rather secondary, but that is not a view held by everybody as you know.

GW Now, let's turn really mainly to your research side because it is fascinating to me that you did your house jobs in Sydney at the Prince Alfred then you went to Pansy

Wright for a year knowing that you were coming to Oxford to Florey. Presumably nothing in that year with Pansy Wright led to your particular turning towards cell biology.

HH No, no, there I was a kind of electrolyte physiologist. I was interested in renal failure and what happened to the salts in the blood when the kidneys packed up. There was a unit down there – there still is a unit that is much involved in this kind of physiology – and I think the first flame photometer, this gadget you use for measuring sodium and potassium, that there was in Australia was in Pansy's department, so that was where those measurements were made. When I came to Oxford there was some work I had started in Melbourne that I thought might be interesting to continue, and I had a manuscript which I had written and I left this with Florey and said 'What about this?'. And when I did finally get round to talking to him about what I was going to do he said well, he wasn't interested in that because there was nobody in the Dunn School there who knew anything much about that subject and there was no point coming to the Dunn School to do something that nobody knew anything about, and that I should do something that there were people in the Dunn School who… so I could profit by it and I thought that was reasonable. Then he set me as my DPhil project the study of chemotaxis, this phenomenon that… whereby motile cells that are able to move have their direction geared in particular ways by substances in the medium, and the problem there was that there was no really decent method for recording it and by a series of accidents I stumbled on really quite a good way of doing this and produced some pretty pictures. So the DPhil work went very quickly once I'd got the method to work. If you get a new method, of course, you crank out the results very quickly. And then after the DPhil Florey and I had a fairly vigorous disagreement because he wanted me to go one way and I wanted to go another, and looking back on it, you know, there was an element of justice in what he had to say, but it… the methods were simply not available to do what he wanted. He wanted to purify certain tissue products because of the penicillin experience, purification was in the fore, but it wasn't until twenty years later that methods became available that would make that plausible. Anyhow, I thought it was a better job for a chemist than for me. So we had a tremendous row actually and communicated with each other by letter for a bit and...

GW He could be very tough couldn't he?

HH Oh yes. He was tough.

GW You too.

HH Yes, but the back streets of Sydney had made me pretty hard to devastate, so I think it was diamond cut diamond. It was rather interesting, I went home and said to my wife that we were going to have to go, I can't stick this. And Florey wouldn't see me for about ten days and then finally I wrote a letter saying that I wanted to see him because I wanted to know whether I was coming or going and looking at other possible jobs. Then he did finally see me and he said, 'You wanted to see me?' and I said, 'Yes I want to know whether I have to leave or not.' He said 'Harris,' – he had this gravel voice – 'you need a holiday, you've been working too hard. Now you go and take a holiday and then come back and see me.' So I knew that I had won through. I did take a few days holiday and came back. Then he said okay, you go and do what you want to do but you are on your own, I remember his phrase: but you are on your own. I later learnt, many years later, that in that period when we weren't talking to each other, he had gone to Ted Abraham, who... Florey didn't know any chemistry worth knowing and he relied on Abraham for chemical advice and he had asked Abraham for his assessment of the do-ability of what Florey wanted me to do and Abraham fortunately shared my view, and Florey came round to accepting that. The magnitude of Florey came out later. I mean once I got going on my own line he stood back and wanted to see where it went. If it had failed I would have been out, certainly. But when it went pretty well he then became very interested and he began to talk to me and would come in, in the evenings. He had a terrible home life and he didn't like going home. He used to come into the lab and talk to people late at night. I was often there and he became a patron and a very loyal friend, and I think the loyalty was reciprocated. He was very tough. He was never my scientific mentor in the sense that I don't think he ever taught me anything in the technical sense. He taught me some attitudes to science; he taught me some attitudes as to what was important and what wasn't important, what was honest and what wasn't honest. But he certainly was a patron who backed me and gave me everything I wanted and was terribly pleased when I succeeded to the chair [of pathology].

GW What went into your mind when you opposed what he wanted? What did you want to do and what led you to want to do it?

HH Well, again it was rather primitive, rather like my romantic decision to do medicine. I wanted to have a crack at the cancer problem from way back, from undergraduate reading, but because I thought the cancer literature was so appalling and I thought the quality of the stuff was so awful. I thought I could do something with this but what I thought I would like to do was start having a look at some multiplying cells. The trouble with the chemotaxis stuff was that it was all done with white cells of the blood that don't multiply, they were all non-multiplying populations. And what I wanted to do was not to compare cancer cells with normals, which had been done *ad nauseum* and got nowhere: what I wanted to do was work out precise good quantitative methods for comparing normal cells which do multiply *in vivo* and *in vitro* with normal cells under the same conditions that do not naturally multiply. I wanted to compare two natural normal populations, one of which was geared to multiply and one of which was not geared to multiply. I had certain questions that I wanted to ask and so I worked out methods for handling these populations. They were not available at that time, now they are all absolutely routine, but at that time I had to work them all out. And so I started to have a look at this general question and then I got deeper and deeper into it. But I suppose the experiment that people associate most with my name is the cell fusion experiment and that came another way altogether. Do you want to know about that?

GW Yes I do indeed.

HH Well...

GW I remember, if I may interrupt you for a moment, that you came to a conference I organised in New Delhi in '69, I think. You had at that time, I think, fairly recently become a Fellow of the Royal Society and if I remember rightly you were talking about hybrid cells in the paper you gave on that occasion.

HH Well, about 1959, Florey's plans for Canberra had collapsed for the Australian National University and he didn't know what to do with me. There was no job in Oxford and I didn't know what was going to happen. I was going to go to the States, with a view possibly to emigrating, because I was open to offers, and then curiously enough I got an offer of a job from what was then known as the John Innes Horticultural Institution. For a chap with my background that was extraordinary, but this was largely financed by the Agricultural Research Council, and both Hans Krebs and Peter Medawar sat on it and both of them knew about me. And at this place they had just put up a new building called Department of Cell Biology. I think it was the first department of cell biology in the world under that name.

GW Was it meant to be for plant cells?

HH Well, originally I think it was meant to be for plants, but the director Kenneth Dodds wrote me a letter, I think at the suggestion of Krebs and Medawar, and he asked me whether I would be interested in this job. So I went down to have a look at it, not thinking that this was an appropriate thing for me, but there was this marvellous new building in the wonderful estate of Bayfordbury [Hertfordshire], beautiful, rural countryside and artificial lake and so on and I was hooked, and I won't go into all the soul searching, but I accepted this. I had already agreed to go to the States for a bit. I went to the States for about nine months. I came back to be head of this new department of cell biology and while I was there John Fincham, who is, as you know, an eminent geneticist, plant geneticist fungal geneticist, became the head of the department of genetics and he was working with *Neurospora*, the classical genetical object of mould. And in *Neurospora* the hyphae, the branches fuse together to make what are called heterokaryons, that is the two different kinds of nuclei, they are brought together within a single cell, and this is a normal parasexual process in *Neurospora*, it does this naturally. And he was working using this phenomenon to study certain genetical things, and it crossed my mind then that it would be marvellous if we could do this with our cells, because the great strides in our understanding of cell organisation in bacteria and fungi all rested on genetic methods, because bacteria did have a sex life, they exchanged genes, and fungi had sexual and parasexual processes, fusion… and I thought if I could actually do this with our cells, which were the ones I was really interested in in the end, this would be a great revolution. So it just kept buzzing around my head and I couldn't see how you could do it because in fungi evolution had evolved this mechanism, it served an obvious function, whereas in the cells of the body it wouldn't have served much of a function because they were all to the first approximation, genetically identical and why bother.

GW Which cells of the body were you…?

HH In general. I was working with various cells from epithelia or cells from fibres, but you know wouldn't it be wonderful if we could introduce genetic methods into that field of mammalian cell biology, which was simply nobody could see anyway of doing it. Then three papers appeared in *Experimental Cell Research* by Japanese group headed by Okada in which they were studying what was a very old phenomenon and that is the ability of viruses to produce multi-nucleated cells, and I knew about this in a general way from the medical background. I knew about multi-nucleated cells, multi-ncleated giant cells and multi-nucleated cells in measles and so on. But Okada was working on a particular virus which they called HVJ, hemagglutinating virus of Japan, and that virus fused very effectively and very quickly and they were also able to show, Okada and Tadokoro,[4] one of his colleagues, you could actually inactivate this virus with ultra-violet light and it would still fuse even though it wouldn't multiply in the cells. So then the penny dropped and I said well that is the way to do it if we can use this to impose a form of artificial sexuality on these cells, and I have a little book in which I note these things down and I noted down that this is the thing to do, but I did nothing about it. Why, did I do nothing about it? Well, I wasn't a virologist and there was no virologist at the John Innes. I didn't have the egg techniques for growing the virus and titrating... That was no problem really I could have gone to Mill Hill which was forty minutes away to the National Institute [of Medical Research] and got the virus. I had other things to do and I was very busily involved in other problems which were... I thought very important, which were very important. Then Florey retired early to become the Provost of Queen's [College, Oxford] and I was elected eventually to take that chair, and during that brief period that I was away from the Dunn School, John Watkins had been appointed to the staff of the Dunn School and he was a virologist and he had all the egg techniques and he had all this stuff. So very shortly after I had settled down and got things going I called John up and explained to him what I wanted to do, and I gave him the reprints that I had written for and got from Okada about the Japanese papers and I said that's the way I would like to do it, can you get hold of that virus for me and grow it up. And he wrote to Periera[5] at Mill Hill from whom I could have got the virus earlier, but didn't. And Periera said he didn't have HVJ, but he had something called Sendai, which he thought was the same virus and he sent John Watkins Sendai and John grew it up and titrated it and so on. Then I decided what two cells we were going to fuse and I went the whole hog. There were some technical reasons for this. I wanted to fuse across species. Why did I want to fuse across species, that is two different species, man plus something else, not simply to drive the media people, the newspaper people out of their minds, which I succeeded in doing, but because in order to do genetics you have to have what geneticists call markers, that is some phenomena, some characteristics that are identifiable between the two parents, and within the one species there weren't very many that you could examine *in vitro*, but of course if I could cross human with mouse, there were thousands of them. And I actually chose a human cell and a mouse cell for three reasons: a) I

[4] Okada, Y. and Tadokoro, J., 1962. Analysis of giant polynuclear cell formation caused by HVJ virus from Ehrlich's tumour cells. II. Quantitative analysis of giant polynuclear cell formation. *Exp. Cell Res.* **26**:108-118.

[5] Helio Gelli Pereira FRS (1918-1994). Member of scientific staff (1951-73) and head of Division of Virology (1964-73) at the National Institute for Medical Research, Mill Hill, London.

wanted to cross species, so that I would have a lot of genetic markers. Then there were technical reasons why this particular mouse cell and this particular human cell would be good – well the main reason was that their nuclei looked very different and we would know whether we had brought it off. The third one was rather irrational, but quite deeply held view of what I regarded as important in science. What I have always liked about science, the great scientific experiments and contributions to me are those that actually change the way we look at things, like Darwin. That was the era of the uniqueness of the individual… I mean Peter Medawar's phrase; everybody was… everything was so specific that you couldn't even cross from me to you and so on. I took the view that all of these phenomena were… had to do with specialisation of the surface of a small family of cells and they were latecomers in evolution, but the way I looked at the cells that once you could get under the skin, they all looked very much the same to me and I firmly believed that they would accept each other if we could fuse them. So that in choosing man and mouse I deliberately chose two cells, from two species that poets and so on always regard as type cases of antitheses, I mean man and mouse. So there was slightly cocking a snook at a view of the world.

GW Pretty characteristic, if I may say so.

HH And so I did, and it worked first time off and we showed that we…

GW The cells were where in this case?

HH Well there was a human uterine carcinoma cell called HeLa and a mouse mammary carcinoma cell. We got on to normal cells later, but to begin with we used these two malignant cell lines.

GW With the Sendai virus?

HH Yes, and we fused them together and very quickly showed that they did accept each other, and that within these cells the genes of both man and mouse were transcribed and the relevant proteins were made, and that the nuclei would divide and eventually that a mononucleate hybrid cell would be derived from this fusion, which combined within a single nucleus human and murine chromosomes and they would accept each other, and so on. We cleared that ground fairly quickly and then we sent the paper off and it appeared in February 13th, I think, in an issue of *Nature*[6] and then the press went crazy. There was a cartoon in the *Daily Mirror* and the world generally extrapolated from the cell experiment to chimeric animals and so there were these fellows at Oxford making the usual medieval…

GW Four-legged man…

HH All this stuff, and then it went around the world and the further it got away from Oxford, the more hilarious it became. My friends used to send me cuttings from the

[6] Harris, H. and Watkins, J. F., 1965. Hybrid cells derived from mouse and man. Artificial heterokaryons of mammalian cells from different species. *Nature* **205:** 640-646.

Buenos Aires Daily News; by the time it got down to Tristan da Cunha, it was quite unbelievable. So that started off a sort of great bandwagon out of which, eventually, somatic cell genetics as a discipline was evolved. And there again I had to make some choices about what I would do, but it was obviously a good start out, there were hundreds of things to do, and which are the ones that you are going to do. And there were certain obvious things to do, which I didn't do because I knew they would be done, and I choice to do something which was quite tough and that was to try to get back to analysing what it was in a malignant cell that made it a malignant cell. I then used that technology to analysing in greater and greater depth what it was that determined…

GW The control process.

HH The control process, and on that I am still working and it still seems to be yielding interesting information. So that is how…Funnily enough… do you know Jack Harley? He was professor of forest science at Oxford, a very…

GW Oh I do know who you mean, yes.

HH Jack told me later that when it was announced that I had succeeded Florey, that I had come from the John Innes which was botanical place, that one of his colleagues had actually said, 'Who is this obscure botanist whom they have appointed to succeed Florey?'

GW That says something for you, that in four years you had become at least a botanist.

HH Yes that was an obscure one. I actually worked on some plant material and I had some plant material going in the Dunn School, because plant cells did lend themselves to certain, technically, to certain kinds of experiments that were difficult to do on animals, especially the giant cells like *Acetabularia* and so on, where you could actually pull things in and out and I actually had some seaweed and so on growing in the Dunn School. It was very good for a department of pathology to have a bit of chlorophyll around, otherwise your mind narrows a bit. So that is my highly eccentric career. I did medicine to become a writer. I did pathology to become a botanist. I did botany to become regius professor.

GW I think in *Who's Who* you give your recreation as history. Do you write about it?

HH A little bit. That has a curious… in Australia no building antedates the middles of the nineteenth century and any Victorian piece of Victorian gothic is a national monument. So I had not really seen any old buildings until I had come to Europe and I done… the one barbarism in my secondary education was that at the end of the first year, you could either choose to take a second language, which was either German or Greek, or you could do history, but you couldn't do history and a second modern language. I thought I would take a second modern language, so I started to read German and I didn't read any history at school, and didn't in fact start reading history until I came over to Europe and saw these old buildings and didn't know what it was all about. I mean I had some vague general idea and I then became very interested especially in medieval history really. Although I am not a good Latinist, I can slog along a bit and over the years that has stuck and I have continued to read… I have not written on medieval history, I have written about other bits of history but I continue to take an unprofessional, but quite consistent…

GW Your ambition, original ambition to be a doctor-writer has still to come?

HH' Well, I have written a few non-scientific things which have been published and I have just written – it's just gone to the OUP [Oxford University Press] – a totally non-scientific book, totally non-scientific, well, I mean non-scientific enough, but I am not going to tell you what that is. So I still, I still… oh, I don't know… I have a daughter who is a novelist and is a good writer, and I think my interests stay too close to reality for me to be a good imaginative writer – I mean fiction writer or something like this, but I enjoy the exercise of writing, not simply scientific papers, which are formal…

GW From the imagination…

HH Yes, and I don't stop to write. I just write as my minutes, hours or weekends appear. I wrote this thing and the OUP liked it and well, you will see it by the end of the year.

GW Well, I'll look forward to it very much. Perhaps a bit unfair, you have just talked about being a realist, but could I encourage you perhaps to speculate a bit about how you think developments will proceed with the work that you have been associated with mainly.

HH Well, I think that the most important thing that happen – my view of it – is that understanding has deepened. And when one looks at the revolution in biology in my lifetime we simply don't think about things in the same way as we did as when I started. We use a completely different vocabulary, completely different intellectual framework, and of course there is always the temptation to say: 'What use is all this, does it cure a disease, or, you know, has it made anybody feel better?' The answer is briefly, yes. I can enumerate the diseases and the way in which people feel better, but that is not the important thing. The important thing is that all the people in this whole business of advancing knowledge in medicine or biology just think and operate and talk in a completely different way. And I think the fact that one has been able to introduce genetical methods into the analysis of somatic cells has completely changed the way we think about somatic cells: the fact that you can cross species and all this kind of thing; the fact that you can put any bit of DNA into anything and have foreign in doesn't much matter. All those intellectual barriers have to come down before people would try these experiments because there was a block, people didn't think they would have any hope of working. In the cancer business I think nobody has a drug just around the corner that is going to be about a panacea for cancer. But, again, we talk about this disease now in a completely different way, and we are progressing very rapidly to a much deeper understanding of what has gone wrong and what is going on. I mean if you attend, which

I never do, but if you were to attend a cancer congress now and hear what is being said about cancer cells with what was being said at these congresses ten or even twenty years ago, it's is completely unrecognisable. So that as one understands more clearly what is going on, so one enormously increases the possibility of doing something useful about it in ways that one can't foresee. Of course, one can never exclude the possibility that some magic potion might drop into somebody's lap by complete accident whatever. I mean this can never be excluded, but you can't spend you whole life sitting in a chair looking at your umbilicus waiting for luck to strike, I mean that is a pretty unintelligent way to spend your life. So I think the important thing that has come out of it is that it has changed the whole intellectual climate of studies in this area, and that we will surely within a finite number of years have a very clear idea of what the determinants at the cellular level are that are responsible in a crucial way for determining this aberration of behaviour. When we have that, of course, we can think in much more concrete terms of what we might do about it: what kind of molecules might do this or do that, or how you might interfere with that, or how you might move this up or that down and so on, and do useful things. That of course is the rational approach to providing therapy and it doesn't always work, much of it comes by chance, or comes by screening or so on – and I don't look down my nose at screening operations, except that they have to be large scale and very professional – but every now and again very important developments occur by the exercise of rational enquiry. I mean, for example, captopril and the anti-hypertensive agents, these were thought out and they didn't happen by chance. They thought it out from the basic molecular biology of the enzymes involved – enormously important drugs. And other than praying for rain, I mean I think the thing to do is just to dig deeper into our understanding, and I have every confidence that as that deepens so opportunities for therapy and diagnosis will flow from it. It always has been the case. In some cases it already… I mean one could talk about certain cancers that… where this is already the case, but as a general problem that, I think, is what I think will come out of it. What gives me pleasure – and it is a rather indefinable thing, but has to do with my personality and my background or whatever - what give me most pleasure is that I think I was involved in changing in a quite dramatic way, the way people thought about these kind of cells, and the media helped. I mean they made a great fuss, but in a way they didn't help either because they scare people, and they exploit the sensational aspect of it and sometimes that isn't helpful. But nowadays nobody thinks twice about putting a gene from a plant or animal… it is a completely open field, but in 1965 if you had asked any biologist around what the chances were, even if you could do it technically, of human and mouse genes operating amicably together within a given cell, they would have thought you were off your nut. I was off my nut but I was convinced it would work.

GW Or even more than ten years later I remember in GMAG [Genetic Manipulation Advisory Group] the opposition to any possibility of species or interspecies…

HH That's right. So I mean I think… it seems to be my fate in science very often to see things a bit differently and sometimes I have been wrong, it's part of the business. It's not simply iconoclasm, I think it runs fairly deep. If I see a sort of placid sea of acceptance or certain points of view it makes me wonder whether we are right. I mean I just…there is a phrase, you know, "thirty million Frenchmen can't be wrong,': yes they can and often are! I mean that sort of… so what I take greatest pleasure in is changing the way people think.

GW Well, you obviously are very far from stopping doing that.

HH Well, I have been very lucky. Most of my, or many of my colleagues have chosen another route at a certain stage in their life, they feel that they have larger contributions to make by taking larger administrative national roles and things of this kind. It is very laudable that they have done this, they are very important jobs, but I have retained a certain infantilism, I think, and there is nothing wrong with being a scientific manager, I just don't find it as interesting as being a scientist. So I continue to do experimental work and haven't got heavily involved in the national administrative, scientific administrative scene. I mean, I pull my wait in the system and I have served on these various bodies, but it hasn't been the centre of gravity of my life; that remains the laboratory and that will, I think, so long as hand and eye and brain remain intact and continue to be so. Of course, the trouble is your…my colleagues are very kind; they won't tell me when I am making a jackass of myself, they will be very kind. I have to have some more objective criteria as to whether what I am doing continues to be useful, and I have some criteria like whether I publish papers under a single authorship not multiple authorship, and whether they get accepted and whether they get discussed and whether they get taken seriously. So long as that happens, I'll keep it up. Perhaps you will tell me when it is time for me to stop.

GW I can tell you now when it is time to stop, but only to say really how enormously grateful for myself and for the College. It has been fascinating and I am sure that this is by no means the end of the story and I look forward someday to hearing a great deal more from you.

HH Well, thank you Gordon.

GW Thank you very much.