Andrew Read

Personal Details

Name	Andrew Read
Dates	Born 07/07/1939
Place of Birth	UK (Gloucester)
Main work places	Manchester
Principal field of work	Human molecular genetics
Short biography	See below

Interview

Recorded interview made	Yes
Interviewer	Peter Harper
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Edited transcript available	See below

Personal Scientific Records

Significant Record set exists
Records catalogued
Permanent place of archive
Summary of archive

Biography

Education: Trowbridge Boys' High School & Royal Grammar School, Newcastle on Tyne. Foundation Scholar and Hutchinson Student, St John's College Cambridge 1958-64; BA 1st class honours, Natural Sciences 1961; PhD 1964.
Postdoctoral fellowships Max Planck Institut fur medizinische Forschung, Heidelberg and School of Molecular Sciences, Warwick University
Staff Tutor in Physical Sciences, Manchester University 1967-77
Lecturer, Senior lecturer, Reader in Human Genetics, Dept of Medical Genetics, Manchester University 1977-95.
Professor of Human Genetics, Manchester University 1995 - (Emeritus 2004).

I set up one of the first National Health Service DNA diagnostic laboratories in 1981, now one of the two UK National Genetics Reference Laboratories. My research has been on mapping and identifying human disease genes, with special emphasis on genes responsible for hereditary deafness syndromes. I have taught on a wide range of courses at Manchester University, elsewhere in the UK and abroad, to clinicians, scientists, counsellors and others. I am co-author of two of the standard textbooks in the field, *Human Molecular Genetics* by Strachan & Read (Garland, 4th edn 2010) and *New Clinical Genetics* by Read & Donnai (Scion 2007; 2nd edition in preparation). Both have been translated into many languages. I was chairman of the Clinical Molecular Genetics Society and founder chairman of the British Society for Human Genetics. In 2007 I was co-winner of the Education Prize of the European Society of Human Genetics.

INTERVIEW WITH PROFESSOR ANDREW READ, 6th FEBRUARY, 2007

PSH. It's Monday 6 February 2007 and I'm talking with Professor Andrew Read in Manchester at St Mary's Hospital. Andrew what I would like, if I may, to do is to start a bit with you yourself and then ask you a bit about how you have seen the evolution of human molecular genetics in general. But just to start with, can I ask, where and when were you born and brought up?

AR. I was born in Gloucester, but my father had a job that moved him around, so basically I lived almost everywhere except London. We moved around quite a bit; I ended up at school in Newcastle and then went to Cambridge, spent 6 years there, did a first degree in natural sciences as an organic chemist. Did a PhD as an organic chemist but working on nucleic acid chemistry because of course that was Todd's department, so that was the exciting thing. Well the truth is that the reason why a friend of mine and myself chose the supervisor we did, who was Todd's right hand man in the nucleic acid work, was just because he was such a very nice bloke. You know Todd had this enormous series of papers that couldn't happen now. I think they were just called nucleic acids one, two, three. four and they went up to fifty something I think.

PSH. I saw it. Looking at PubMed I saw your very first publication picked up in 1965 and it's Nucleic Acids 49. I was wondering whether that was real or whether it was some kind of misprint.

AR. No that is real.

PSH. Or volume of the Journal.

AR. No because Dan Brown who was Todd's right hand man in all of this and he was my supervisor, was a very nice chap.

PSH. Just backtracking a little bit, was there anybody in your family or early life that particularly gave an example or encouragement to go into science?

AR. Absolutely not, really. No, in fact almost the reverse because my father was a historian, that is to say he had a degree in history and he was originally a senior history master in a school and subsequently became an HMI specialising in history. He was perfectly good natured, but he was always somewhat dismissive of my scientific interest, but I was the sort of boy who had a lab and made bombs and attempted to make rockets and so on. The other thing was, I was very, very interested in collecting butterflies and moths and of course back in, we are talking the early fifties now, E B Ford wrote his classic New Naturalist books on butterflies and moths which contained quite a bit of genetics in them. So when I was still in school I was doing Mendelian breeding experiments with butterflies and moths, although I never actually did any biology whatsoever at school. One of the things that I have always been half pleased and half amused at is the fact I have never ever had a lesson in any branch of biology from anybody whatsoever at all in my life. It was chemistry, physics and maths at school. I did chemistry, with physics, maths,

biochemistry as my subsidiaries at college and I never did do any biology whatsoever, but I did have that interest in moths and so on and I did know my Mendelian genetics from those days.

PSH. Do you think that might have been one factor in, later on, you being interested in taking up opportunities in the genetic field?

AR. Possibly it was, but it was a pretty minor thing. What happened was, as I say, I ended up working on nucleic acid with this organic chemist in the Lensfield Road labs in Cambridge, which was Todd's labs and did a not terribly distinguished PhD. I did a couple of post docs in Heidelberg and then in Warwick, but my life was in rather a mess in those times. I got very disillusioned with research and I really did not want to go on in research. I ended up getting a job in the extramural department at Manchester University with the title of Staff Tutor in Physical Sciences, which actually was initially a very nice job because what the job involved... I mean, in those days there was a far more serious commitment to adult education than there is now, and it wasn't just earning money from putting on courses. There was a Government, Department of Education subsidy for liberal adult education courses which came to universities and there were also extramural departments who ran those courses and also ran the whole string of vocational courses which would have to be self financing. They were staffed by about twenty people whose titles were Staff Tutor, Senior Staff Tutor and so on, that was equivalent to Lecturer, Senior Lecturer and so on, and it was like a mini university. It was rather nice because you had people from every branch and in some respects it was a leisured existence, if only because we all worked most evenings and therefore during the day you felt you were a bit more your own master. Coffee time conversation was the highest level and best coffee time conversation I've ever had.

But what the job meant was that I had to organise the programme across the range of physical sciences and to do my own teaching in it, some of which was non vocational plus some vocational. It meant I could take an interest in a rather wide range of things, which suited me rather well. I actually did that for ten years but the problem with the job was it was completely non progressive, so although in theory, ideally you should do research, that wasn't actually realistic. What one was doing, you know, people might write the odd article or something but they weren't seriously involved in research, so I did begin to feel rather trapped in that. At the same time I had got steadily more interested in genetics, initially from a molecular biology standpoint I guess. I had a very good friend who was a lecturer in molecular biology in Edinburgh, which was a very leading department. Things were pretty easygoing in those days.

When I was a post doc at Warwick, that was one of the new wave of universities founded on enormous enthusiasm and money was being thrown at them and there were some rather flaky ideas around the place really. The man who ran our School of Molecular Sciences was a very very bright man recruited from Cambridge. He was an excellent organic chemist but actually he had absolutely no conception of what went on in living cells. The departmental project was to model oxidative phosphorylation and this was pre Mitchell chemi-osmotic days, so we had wonderful schemes of oxidative

phosporylation involving the latest schemes of curly arrow pushing around chemical formulae and so on, and my job was to make one of those things work and to produce ATP in the test tube by oxidising something or other through a series of chemical coupling things. It didn't take too long before quite a lot of us were fairly disillusioned about what we were doing. This was '65 to '67 that I was there and I think there'd been a big international congress of biochemistry in Moscow in '66 and people had decided they were going to sink this wretched Mitchell man, who was a nuisance and was putting up stupid crank ideas. So they all trooped off to Moscow to shoot down Mitchell and they all came back with their tails between their legs, and Mitchell had shot them down. And so there was something of a crisis of confidence, at least in the lower levels in our department.

Meanwhile my friend had got a job as a lecturer in molecular biology at Edinburgh and he was doing bacterial and phage genetics and I spent a lot of time actually up there working with him in the lab. I taught myself bacterial and phage genetics and found that jolly interesting, and I sort of slowly climbed the phylogenetic tree, because basically if you want to use that sort of knowledge in an extra-mural context you need to talk about people not bacteria. So that was how I started getting interested in human genetics and I suppose coming back to the butterflies it no doubt helped that I did have that background.

I started coming to seminars in medical genetics because it was quite obvious that those were the most interesting and exciting seminars going on in the university. So I became gradually a bit of a fixture at these seminars and then there was a very strange occasion when Rodney Harris was doing a seminar on population genetics. Rodney didn't really know an awful lot about population genetics but he was doing his best and I as a young twat kept interrupting and so on. In the end he said to me 'why don't you take over?' I was left with an audience, a carousel full of slides I hadn't seen. What Rodney didn't know and what the audience didn't know was that the slides were taken in sequential order from Cavalli-Sforza and Bodmer, Genetics of Human Populations, which was the one book that I had really put a great deal of work into. I used that as my way of actually getting some proper understanding of the thing. So I think Rodney was very impressed at the way I was able to turn these slides I hadn't seen into a coherent lecture and I think it was probably that that led to him to agreeing that I could do a sabbatical year in the department. We weren't entitled, but there was a presumption that one might take a sabbatical term every three years or a sabbatical year every ten years and I'd just about knocked up my ten years and hadn't used up any of that, so I applied to do a sabbatical in medical genetics and I sort of came and never went away again. So that's what happened.

PSH. So I am trying to think when that sabbatical year was and what stage medical genetics had reached. Was that about 1980?

AR. No no no, sorry '76-'77. I think that's right. I'm not even sure where I could check it but I think that's right.

PSH. So just before molecular genetics really was coming along.

AR. Yes, molecular genetics didn't really exist then. When I came into the department, I don't know what Rodney thought, but my feeling was that the skills that I could bring were primarily in computers because I knew a bit about how to use and programme computers and of course desk top micros were just coming in then. I suppose some theoretical knowledge both of chemistry, and the mathematics of genetics, because actually there was nobody in the department who had much sound theoretical knowledge of genetics and obviously people coming through medical genetics would probably not have been too happy talking about Hardy-Weinberg, and so on. The first thing I did when I came into the department was to order a large floor standing computer terminal which worked through a phone line up to the university computer centre.

Manchester has always been the forefront of computing. The Manchester computing centre had probably the best academic computing facilities available anywhere. In those days you had your typewriter keyboard connected through a phone line to this thing called George III which managed your stuff. So initially I was looking for areas of data handling in the department that obviously cried out to be computerised, and the obvious one was the amnio follow-up because we had a very very good lady who followed up all the amnios with enormous determination and produced a wonderful data set. It existed on deck after deck of punched cards which you sorted with a knitting needle and which were getting well out of control. So I guess the first useful thing I did in the department was to get that all computerised and to write programmes that allowed one to get the information out of that. And for years and years I shared an office with this lady and once a week I would fill in coding sheets from her punched cards. I would take them up to the computer centre where they would punch them onto computer readable cards. I'd update the database. I would run off an analysis of it and so on. So that was the first vaguely useful thing I did and because of that computer thing, I got involved early on in the vitamin trials because they needed someone who would do the statistics, and Rodney always claimed I was the man who understood computing and statistics. As far as the statistics went, it was a complete lie, but on the other hand since the stuff stopped on my desk I had no option but to get down to it and sort it.

PSH. That's interesting. What was Manchester's particular role in the neural tube defect vitamin studies? Was it as part of the multi centre MRC study or was it before that?

AR. Not MRC. No it was before that. It was Dick Smithells originally, I mean he'd published studies from Liverpool where he'd retrospectively analysed stored serum samples from women and subsequently shown those who had had babies with neural tube defects had levels of various vitamins which were toward the lower end, though it was not at all predictive. I was not part at all of the things that led the setting up of the multicentre study but at the time that Rodney asked me to join, there was Dick Smithells, there was Mary Seller at Guy's. There was Norman Nevin in Belfast, there was Dick's own set of people in Liverpool.

PSH. Was it Liverpool or Leeds by then?

AR. Sorry Leeds. Who else was involved in it?

PSH. I think that was about it from my memory. So you were there at the point when that multicentre study was cranking up.

AR. Yes, I have to say I had no part whatsoever in the design of it and . . .

PSH. Well that's probably not a bad thing.

AR. Well I learnt a lot from that. I really did. I learnt a great deal from that.

PSH. Is it true, as I have heard anecdotally, that they did want to make it a double blind study but were refused Ethical Committee permission, or was that just a rationalisation?

AR. I was told that story by Rodney and I have to say I would not like to put much money on it. My own belief is that, I mean it was quite difficult finding an adequate number of women. I don't think anybody thought that the effect would be so dramatic. Certainly my thinking was any effect that there would be, you are going to need every woman you could possibly get to be able to detect it. Though, as I say, I had no part in the design I think I might well have argued for a non-randomised trial, partly from inexperience, but partly from the belief that we were going to need the maximum possible number of women on the vitamins. So the other reason I suppose why Manchester was involved, was we did have this very good follow-up scheme, and the amnio follow up meant that we had good access to large numbers of women who had had amnios with previous neural tube defects, so we could sort that out and we had a health visitor, Mary Weetman, who was the point of contact for recruiting these women, so I guess Manchester was well placed to contribute to this study.

PSH. So what point was it when you started to be able to get involved with molecular aspects as part of medical genetics?

AR. Well, when I first came into the department there was nothing molecular that I could usefully do, but on the other hand I did have this feeling it's got to come and I thought one of these days they are going to be quite glad to have someone with a decent training in chemistry in the department, and to some extent I did try to create molecular opportunities. In fact that first came because initially the main thing I was working on was neural tube defects and various aspects of the follow up, but I introduced the acetylcholinesterase test into the department and that was a gel electrophoresis test. One of the reasons I was keen to push that was because it actually involved the lab people doing something that looked a bit molecular. I didn't have wonderful foresight but I thought that it's no bad thing that one should take that step. Of course the only lab . . .

PSH. When you say lab people, who were the lab people apart from cytogeneticists?

AR. Full stop. Well no, we had the tissue typing lab within the department which existed in two separate branches because there was one lot who did the straight matching and there was another lot that did lymphocyte cultures; I think largely for personality reasons they'd diverged from each other. But they were a really quite separate thing. Obviously they were there because of Rodney's long standing interest in HLA. No, the only lab within the part of the department that I was in was cytogenetics, and I was very aware that although they were obviously frightfully good at what they did, if you asked them to calculate the molecular weight of sodium phosphate they would look at you blankly. So I felt there was actually a job to be done in trying to get a bit of chemistry in there. So we worked on the acetylcholinesterase tests and of course you discover who it is among the cytogeneticists who take an interest in that sort of thing, so I ended up collaborating particularly with Jonathon Waters who was with us, who seemed interested. So when it finally, when DNA began to dawn, I'm really not too sure what year it is. I suppose you can look it up. It was either '81 or '82. I think it was '81 but I wouldn't like to swear to it but anyway Rodney suggested I go to Leiden where there was one of these Boerhaave courses run by Peter Pearson and Bert Backer on DNA things. And I went to that and we spent, I think it was two weeks, it might have been three, extracting DNA and running gels and doing Southern blots and so on, which despite the fact I had a PhD in RNA chemistry there wasn't a single aspect of that that wasn't completely novel to me, including even handling Gilsons, because we had never used those when I was a PhD student, so it was essentially completely novel, although obviously I had some theoretical background in it. Having gone on that, there still wasn't really at that stage I think, any clear practical application, although one could see it's got to come. But having got back in the department I then set about with Jonathon Waters in establishing a DNA corner in the cytogenetics lab and we spent a bit of time getting it so that we could extract DNA, make gels and run them. I don't think at that stage we ever even got around to Southern Blotting. We were just running gels. It was the Duchenne that really, I think, drove it, because we had this genetic register in the department. I'd also been fairly involved with that because that was another area where I'd been setting up computer systems, so I was pretty familiar with the genetic register and at that time we had I think Duchenne, Huntington's and polycystic kidney disease on the register. It was clear that Duchenne was the one where there was the urgent human need and also the scientific possibility of actually doing something. You probably know better than I do the date when that first linkage between RC8 and Duchenne was first published. When was it?

PSH. It was either '81 or '82. I think the first X chromosome libraries came in 1980 and I think the first linkage in '81 but I suspect the first sort of applied papers were '82.

AR. You know the R in RC8 is Rob, Rob Elles?

PSH. I do. Now Rob of course hadn't come to Manchester at that point. Can I ask you, did you have at that stage any contact with Bob Williamson's lab in London or did that come later?

AR. No we did have contact with Bob's lab. You know Rodney and Bob used to talk about things and in fact it was one of these wonderful missed

opportunities, because Bob had suggested that I should go down to his lab and actually get the stuff that I had sort of half played with in Leiden and get it working seriously through the genetic register. We had been collecting DNA samples - that was something I got set up early on, and we had quite a good set of samples from some big polycystic kidney families and Bob said to me 'why don't you come down to my lab. Bring your polycystic kidney DNA. We've got globin probes. They won't detect anything of course, but why don't you go through the motions to learn how to do it.' And for one reason or other I never actually went. That's actually the second big discovery that I failed to make, because when I was a research student in Cambridge, I was trying to develop a method of sequencing RNA by sequential chemical reactions that knocked off the end nucleotide which you then identified, and so I needed RNA, and I thought the way to get this was, I cycled along to the brewery in Newmarket Road with a big conical flask and they gave me a lot of yeast, so I brought that back and extracted the RNA from the yeast and you ended up with two pots in the end. You had ribosomal RNA and transfer RNA in pots. I then went to the operating theatre at Addenbrookes where some poor man was having his prostate out and got his prostate and extracted the diesterase from the prostate. I left the transfer RNA in the fridge because I knew that was a very heterogeneous lot of stuff. So I took the ribosomal RNA and digested it with my prostatic enzyme and that gave me a series of di-tri- and tetranucleotides which I could then use as material to play around with. Of course had I actually done it on my transfer RNA I would have discovered the CCA ends on all transfer RNAs but I never bothered to do it because I knew transfer RNAs were heterogeneous. So that's two different discoveries staring me in the face.

PSH. Never mind. Two Nobel prizes gone west! Coming back then Andrew to your lab at Manchester. You got things going for Duchenne and am I right that it was fairly shortly after that that Rodney got this Department of Health grant as part of the three centres?

AR. Well the way it started, after Jonathon Waters and I got this sort of very basics of DNA technology working and we had established the start of the DNA sample bank which was linked to the genetic register. Rodney and I then applied to our Local Health Authority because they had the system of locally organised research grants and so we got a grant called Molecular Markers in Genetic Analysis or something like that. Anyway it was a grant for I think two years and that was when we brought Rob in. So Rob joined us from London and he, unlike either of us, actually really knew how to do it and so that was when we first started doing clinically orientated analysis, which I think was Duchenne. I'm pretty sure it was, because I can't think what else it could have been. We weren't doing any haemoglobinopathies in the department and I think that was the only other thing that would have been practical. We did a bit of fetal sexing as well with a Y-probe but basically it was Duchenne. So Rob came, brought some competence in Southern blotting with him, got the Duchenne stuff going and I think it was on the basis of that that Rodney together with you and Marcus got the special medical development grant. So on that we were able to recruit another person, Roger Mountford, who came to us from Leicester, and then as you know from there it more or less took off.

PSH. At what point was it you got interested in the molecular basis of Waardenburg, because that goes back quite a way doesn't it?

AR Quite a way yes. What happened is, initially I really spent all my effort on the DNA lab that we were establishing and trying to get it to do something clinically useful, but I was aware that I was actually being paid by the university and that probably my future depended on being able to get a few publications and do some research and of course the polycystic kidney thing would have been one possible angle for that, but initially I was looking around for a disease that one could map and in those early days, which I think we are probably talking about '82, I thought it was just too difficult to try to map an autosomal disease. Because, you know, it was a good week's work to get your results with any one probe and of course, actually getting hold of the probes always you had to negotiate each individual one and so on, so it really wouldn't have been practical to try to map an autosomal condition at that stage, so I thought an X-linked condition, and we just looked around for clinicians who had families with X-linked conditions where the clinicians were interested and the families looked good enough. Of course there had always been a good bone metabolism unit in Manchester and so they had big collections of families with two diseases, hypophosphataemic rickets and with the Marx's disease, the hypocalcaemic?

PSH. Hypocalcinuria.

AR. That's right yes. So we set about collecting DNA from both of those, although the Marks disease was autosomal. For the rickets, I had a very good clinician, Mike Davies, from the bone metabolism unit. We worked very well with him and between us we got DNA from all the families and then it was primarily Roger Mountford who did the actual hands-on work on that. I was as much as anything interested in it for the linkage methods, because I think that was one of the very earliest attempts at multi locus mapping, because originally one had had just Liped as a linkage programme and then M-link came along and M-link in theory was capable of multilocus analysis and I was very interested in trying to make that work, so the rickets, I saw that as an entry into genetic mapping. Having managed to map that, then we thought well, OK, let's now see if we can tackle something autosomal. The Marx's disease samples were not very satisfactory, and the answer came about through Rodney's interest in deafness because Valerie Newton, who was a clinician in the audiology department, had done a PhD and I'm not sure if Rodney was a supervisor or co-supervisor or advisor or something. Anyway Rodney had good contact with her she had the families with Waardenburg syndrome. I was interested partly because it was clear that these were good enough families that had a chance of doing something, and Valerie was a very, very meticulous worker whose pedigrees were totally and completely believable and whose blood samples really did come from the person who she said they came from. I was also very interested because it was clear to me that whatever went wrong in Waardenburg's, when that gene was doing its job, it was doing a very interesting job. It was clear that it was in someway connected with differentiation of the neural crest, or maybe providing a navigation system for migrating neural crest cells so it was going to be an interesting gene. So it was that combination of practicality and potential interest that made us get going on Waardenburg's and I guess we probably

started that in probably about '88, something like that. I started collecting the DNAs from the families and then I had a grant so I had someone working for me specifically on the Waardenburg project who did that. And then of course there was a famous Japanese patient who had de novo Waardenburg and a de novo inversion, 2q35-q37, so that was why I thought this was an area worth looking at. Of course we tried to get cells from the patient, but they had been signed up by someone at NIH already and been taken on a trip to Disneyland and so on and we weren't going to get the cells. Using that knowledge we had looked with a number of 2q probes and we had established the linkage in about 1990, something like that. It must have been '89 actually because I remember, actually I had had a visiting professorship in Norman Nevin's department and it was at the time I was there that the results came through which, when I ran them, it was clear that we'd had got the linkage and that it was on 2q, so then of course it became, we would have just loved to have got cells from the Japanese patient but we couldn't. It was American Journal of Human Genetics . . .

PSH. I've got one here, '92. That's the Nature paper.

AR. No it was before that.

PSH. It must have been, yes here we are Annals of New York Academy of Science '91. And American Journal of Human Genetics 1990.

AR. That's the one. I think it was '89 probably that we got the linkage and obviously it took off from there and was very interesting.

PSH. At what point did you link up with Tom Strachan and start thinking about a book.

AR. Tom joined the department because I guess Rodney was looking to recruit someone else with good hands-on DNA abilities and quite possibly saw that I was in some ways more a theoretician than a hands-on person, I don't know. So Tom was here in the department, initially working mainly on 21 hydroxylase. I'd written a little book for Gower Medical Publishing called Medical Genetics, a Pocket Guide or something like that, which was a book that rather appealed to me because I have always rather liked little books that have a lot of very cut and dried information, organised very tightly in them. This was something that quite appealed to me. I used to keep little notebooks full of microscopic writing about everything that was known about every butterfly and moth in Britain and so on. All the contents into a notebook one could carry around in one's pocket. And I had had the idea. I would have to think what date it was. I could look up when the book was published, but I had the idea that we were beginning to get some sort of idea about the human genome. Whereas previously, well it came about partly from the teaching, because I was very struck by the fact that if you taught anatomy or physiology or biochemistry, you start by talking about normal and then go on to talk about disturbances. When you teach genetics to medical students you start by talking about diseases and may well never get around to talking about the normal genome, which fundamentally is of course because we haven't got the slightest idea what it did except as chromosomes, but the time had come when I felt we knew enough about the normal genome to make it quite

interesting, to try and write something that was an account of the normal genome rather than an account of abnormalities, and that little book for Gower Medical Publishing was my attempt to do that.

Then later I had got involved as a series editor with IRL Press for a little series of books called I think, Medical Perspectives. That came about because initially Kay Davies and I had been asked to write one on inherited disease, which we had done, so I had had that contact with them. So I had the idea that it would be nice to do one of those medical perspectives books that would be a rather enlarged and updated version of the little Gower book, and Tom and I were the two people who knew about DNA in the department and talked to one another, so it ended up, that I as a sort of Editor asked Tom to do this, so he did that and produced this book, The Human Genome, which, I think by then the IRL press had turned into BIOS, I think that was published by BIOS but again, we can check.

PSH. Weren't IRL press taken over by OUP.

AR. Yes they were and then what happened was . . .

PSH. They split off, sold it or something to BIOS.

AR. Well John Bradley was the one who ran IRL press and I think he was a serial entrepreneur, so I think his reaction was then not to join OUP but to start another small publishing company, so I'm pretty sure that he had some hand in BIOS. I can't remember. Anyway I think this book ended up with BIOS. I have got all the copies at home not here, so will have to check. So Tom had done this human genome book and I suppose we both felt that that was quite a nice approach but Tom must have felt it very constricting to have to try to get it all in that space and I probably felt, why should Tom have all the fun, so I guess that's how the proposal came about.

PSH. It's always amazed me that really, well certainly before and to an extent since, there hasn't really been quite a comparable book [*Human Molecular Genetics*] taking that field as you have done it.

AR. That's right and yes, it is to my mind surprising, although I do think, we are talking early nineties really when these ideas were taking shape and I think in the early nineties there weren't a lot of people who were thinking about the normal human genome. I mean I know of course that the human genome project had been launched, I am sure there were far sighted people thinking a great deal about it, but the sort of every day stuff you got was just catalogues of microsatellites which were then used primarily to map diseases, so I think the focus was very very much on diseases. I think people moved quite slowly and partially to being much interested in the human genome or at least those people who were in the sort of environment that Tom and I were in moved quite slowly to that. So I guess we did almost define an area with that book. We were very lucky. I mean we hit a niche in the market and perhaps because of the success of that book, there hasn't actually been a head on competitor in the 10 years since that first edition.

PSH. So now its edition 3 that's out and you are starting all over again on edition four.

AR. That's correct.

PSH. One thing you have been involved in a lot, Andrew, is the European Society and I have always seen one of your roles as to tie the molecular groups in closely with the more clinical groups in that society, which is important.

AR. Well, I would say that was a role I was very aware of and worked hard at in the British Society, but in the European Society I've not really felt that role. I mean I ended up on their scientific programme committee and then I ended up chairing that committee for a few years and now I chair their annual meetings committee and I'm their treasurer, but I wouldn't say I feel I have that sort of political role there. I mean I have, like so many other people, had periodic attempts to get the cytogeneticists to be a bit more collegial and the latest one was rebuffed just a few months ago. But we keep trying.

PSH. Was that the European or the British?

AR. That was ECA

PSH. Why do you think there has been this fairly major difference in approach between the molecular geneticists and the cytogeneticists in terms of willingness to link together with other groups?

AR. Well, I think you can make kind and unkind explanations of that. I think in the early days I think a lot of it was personalities. I think the people who were leaders in cytogenetics with a few exceptions were people who had fought to get a patch for scientists, and had probably fought their way out from under the clinicians. Because you know, if you think of the early days, you'd got this set of very bright clinicians who came in and whose main scientific work was in cytogenetics because that was all you could do, and I think that the lab cytogeneticists probably had a pretty hard fight to stop just being the technicians for the clinicians. I think that largely happened through various personalities who were perhaps a bit awkward and I don't think they were going to give up that independence very readily. So I think there was that strand to it. I think there was a strand that they felt threatened by molecular genetics, because they had been the lab branch of clinical genetics for years and years and years, and then suddenly everyone was getting excited about molecular genetics and wanting to put money into it and cytogenetics was seen as a bit of a backwater. I think if they had been wise they would have taken over molecular genetics. They did try to actually. They did try to. The reason we set up the CMGS in the first place was because of the proposal by the cytogeneticists to have a society that would be entirely lab scientists and which clearly the cytogeneticists, because they were there and established, were going to lead it all and we weren't going to have that, so that is exactly why we set up the CMGS. So if you like, it was defensive in the first place.

You can also see other quite honourable things. I mean cytogeneticists were obviously very very strongly linked into delivering service and because so

much of what they did was prenatal diagnosis where there was no scope whatsoever for messing about, you'd really got to have tight systems in your lab. You'd got to have very tight quality control, very tight progress chasing, so they inevitably had a very managerial approach to things which was quite inimical to the research mindset. I think it is very clear that there have been extremely few people in Britain in cytogenetics during the 1980s and 90s who were seriously interested in research in clinical cytogenetics. Then I think there's is to some extent a personality factor because if you can spend your entire time squinting down a microscope at the same 46 chromosomes and getting terribly good at recognising every individual band and whether it's in the right place and the right size, well that takes a certain type of personality and so I think cytogenetics naturally brought into it these very careful, perhaps rather unadventurous personalities who, what really mattered was to be 100% reliable. It really did matter. You had to have that thing, and molecular researchers were typically slap happy people. You know, one played around and one did things and one sometimes got things mixed up and sometimes you dropped things and so on. It was a different culture in those early days, because what we were doing was in general not clinically useful. I mean it was much closer to the sort of lads-in-the-lab culture than to this careful meticulous diagnostic culture.

PSH. Do you think that the need in the early years for linkage analysis was another factor perhaps which bound the molecular and clinical geneticists together?

AR. Oh yes, very much so. I mean it could have bound, well not the need for linkage analysis, but the cytogeneticists obviously had natural very close interactions with the clinicians, although of course it's true that a large number of their samples came from outside clinicians, the report went to outside clinicians and the clinicians within the medical genetics department had no knowledge or interest in those, whereas certainly when you were working on gene tracking it naturally created very close links between the clinicians and the laboratory. Certainly in Manchester we had the genetic register and we saw that very much as part of the molecular genetics effort, and we saw the molecular genetics as primarily a tool for making the register more effective. So there was that very tight linkage between them, yes.

PSH. If we look just a bit more widely, even outside Britain at how molecular genetics came into medical genetics and medicine. What do you see as having been the key events that made this transition between a highly basic area of science and something which then became really important in practice.

AR. I suppose the paper that stuck in my mind was Y W Kan back in - when would that have been? Something in the 70/ 80s something like that?

PSH. Yes it would

AR. In fact that was quite interesting, because that sort of hit genetics just after I had moved into the department and I certainly took that as a big harbinger and I imagine that affected a lot of people. I mean I can remember having the arguments even, well, long into the 1980s, whether all this DNA

stuff actually was any clinical use. There was no doubt a lot of people thought it was a fun and interesting academic area with no clinical application. In fact I think it rather parallels the present day argument about susceptibility factors for common disease. I think in many ways the same arguments are running and I'm actually on opposite sides of those two arguments. So certainly the Y W Kan thing I think was important and I think haemoglobinopathies in general were probably really the driving force, because of course while we were playing around in a very uninformative way really with RC8 and L128 and Duchenne, meanwhile of course John Old in the Oxford lab was doing extremely precise molecular work on haemoglobinopathies, so I would guess that that was really what made people realise it was clinically useful.

PSH. From a technological point of view what would you see as being the main changes that really facilitated it becoming a practical lab discipline.

AR. It was a practical lab discipline once you had a decent number of probes with known linkages to disease loci. One would put up with the vagaries of Southern blotting and so on and I think we all lived with that. Certainly in our area, I don't think sequencing was really of any importance at that stage. It was all gene tracking but it was quite exciting times, wasn't it, back in the mid eighties? You got each month, new diseases were mapped and you realised that you could use gene tracking and one spent a great deal of time at the computer trying to do the linkage calculations and so on, which I quite enjoyed doing.

PSH. It was a golden era.

AR. It was, particularly because as we were saying before, it did have that very natural close collaboration between the clinicians and the labs so, I mean at that time I had files which had pedigrees of every family we studied with the DNA sample numbers marked on but also people's names and dates of birth and whether they were affected or unaffected and so on. It wasn't just a sample, you know. I didn't have contact with the patients by and large, but nevertheless you knew the family on paper and it was just natural to sit with the clinicians and discuss where you had got. Of course it's different now. And I suppose it depended partly on people's attitudes of mind and I think again the cytogeneticists tended to be concerned to keep their 'patch' and the molecular geneticists I think, probably as much by luck and by that sort of necessity, I think the molecular geneticists always were much more open to the clinicians. But we took a number of perfectly deliberate and thought-through steps to try and make sure we didn't turn into technicians. One of the early things the CMGS did was to define the job of the lab as being to produce the report with risks, not to report the genotypes to the clinician, and I certainly thought that was a really important point to get over. We were not going to be the technicians who carried out the tests the clinicians asked us to carry out, and reported those results back to the clever clinician who would analyse it, because there has always been that tension hovering in the background. Molecular geneticists have worked quite hard to minimise the conflicts that arise from that while at the same time making sure they are scientists and not technicians, and of course we were helped by the culture in clinical genetics laboratories. But we saw the fights that some branches of pathology had for example, and there was a time when there was this move to get consultant

molecular pathologists which I certainly was worried about. I really saw that as something that might lead to ghettoisation of the molecular scientists and de-skilling of their jobs and I remember spending some time talking to people about what a bad idea that was.

PSH. Looking ahead just for a moment. Do you feel we are a bit of a crossroads now in terms of what you might call microscopic based techniques and more molecular chemical techniques with the new array developments? Do you feel that finally the age of microscopy may be on the wane? What do you think?

AR. Obviously that's something the cytogeneticists lose sleep over or alternatively bury their heads over. Yes, I think one has to say it must be, for all that it is clear that you can find things out by looking down the microscope that you can't find out by other methods, balanced translocations, for example. Nevertheless the difference in cost and speed is just so great now I think it is seriously hard to justify looking down the microscope to do routine antenatal screening for Down's for example. So I think for the cytogeneticists, yes I think that is a problem. Of course they have moved a long way into FISH and so on and at last they are doing a decent amount of molecular genetics, although I don't know in how many departments there is really close day-to-day working collaboration or shared benches or anything. I suspect that is still fairly unusual.

PSH. Coming back to one area which you really have been very much involved in and that is the teaching side. Would you see this as being a development from the experience you already had and the enjoyment you already got out of teaching because you've had this as a major focus all along?

AR. Yes that's true. I always have enjoyed the teaching and yes I guess, I mean when I came in from the extramural department, I had had a heck of a lot of experience in teaching very very diverse groups all sorts of things, and that had been an environment where you think quite hard about what you are trying to achieve and how you set about to achieve it, whereas of course when you are in a very research led environment basically you think of how you can get out of it or dispatch it with the minimum of effort. So yes, I think I certainly came in with a strong pre-existing interest in teaching. I was very nervous about teaching medical students in the early stages, partly because I wasn't a medic. As I say I had never had any lessons at all in biology from anybody, so I was pretty vague about where your pancreas was or what it did and I felt a certain nervousness about teaching medical students, but yes, I have always been interested in that. I also did a lot of teaching for biological science because I thought human genetics is really one of these integrative areas where you can bring together a whole lot of things and pitch it around stories that students just naturally find interesting. So it just seemed to me and I suppose I was just re-capitulating my own experience really. It just seemed a natural way of getting into a whole lot of interesting stuff.

PSH. What about plans for the next year or two Andrew, now you are sort of, in theory, partly retired and now you have got out your book with Di Donnai. Apart from the new edition of Strachan and Read, any specific plans?

AR. Nothing major, no. I mean the Strachan and Read, we are not due to hand over the final manuscript until January 08 but the publishers have been terribly keen that we should have a schedule of chapters to be delivered each month which I must say I don't like but I suppose it does force one to do something, and I sent him my first revised chapter two or three days ago and I am now working on another one, so actually that is going to occupy quite a bit of time.

PSH. How many chapters are there?

AR. I've got, I should remember, 21 or 22 or something.

PSH. With twelve months in the year that does give you a bit of a schedule doesn't it?

AR It does yes, and realistically I'm going to go away for summer holidays in August because my wife still teaches, so our holidays have to be in school holiday time. Allowing for that I have got a chapter a month schedule which, I tell myself it won't all be too much effort and obviously the chapters which will be very current stuff and require a great deal of re-thinking are the ones I have left to as near to the end as possible. Not in order to put them off, but so that it should be as current as possible when the final thing goes in. I can see that occupying quite a bit of time and I still do a reasonable bit of teaching. I'm still, what we talked about this, the Nuffield Bioinformatics working group which is actually turning out to be quite a lot of work because you get loads of stuff shoved at you for reading every day. That's keeping me busy and I wouldn't do it if I wasn't interested in it.

PSH. Have you had a chance in that Nuffield Council forensic work to visit the forensic labs yet up in Birmingham?

AR. That's scheduled for this Friday week so we will yes.

PSH. I went up there and it was an interesting experience.

AR. Tell me more. Tell me what I should, you can switch your microphone off if you want but tell me what I should ask!

PSH. It's a totally different world. This was probably four years ago now, but they are a technically very able set up, but are completely isolated from the rest of the world and at that stage had no concept really that there was need for any ethical scrutiny of anything.

AR. I think they are still there.

PSH. The same person who was director at the time wore about five different hats and was responsible for the DNA bank, the ethics committee and all the other different things. It was quite disturbing actually and we all felt, this was the Human Genetics Commission, that it really needs opening up to the rest of the world.

AR. And actually that has become more difficult now it has all been privatised because there are now a series of different companies doing it and you can see that when they have their proprietary method which they say will give you better things, better analysis of mixtures or whatever, they are not going to really let any outside person properly evaluate that. So I think that is a serious problem. There is still this talk of getting proper regulation and a medical style ethics committee that would overlook the research. I actually myself feel at the moment, although my mind may be changed on it, that people wrongly focus on research being an ethically sensitive area compared to the day-to-day running of the thing. I feel the day-to-day running is really the area that needs much more independent oversight but I have grave doubts as to whether that can be really be implemented given that it's now contracted out to a series of private labs who have their own proprietary systems and who are not going to just tell you everything.

PSH. It will be interesting I think for you to find out what research they are actually doing and what if any oversight it has in terms of . . .

AR. We have tried and made approaches there and got a list of applications that have been made to perform research and who made them and whether it was approved or not approved, but one has to say the actual information contained in those is negligible and is often hard to see through. I mean do you see the research as being a particularly difficult area?

PSH. I think some of it is very sensitive. This research linked with potential criminal aspects of individual genetic diseases.

AR. Tyrosine hydroxylase, dopamine receptors etc.

PSH. Anyway you will see. Just to finish Andrew, and we must finish, I have been asking everybody I see two questions, and the first of these is whether there's been a particular person who has been a special influence in your career or the development of your career in medical genetics that you feel stands out?

AR. I would have to say Rodney Harris because he took me on largely through blind faith and he has actually always been very, very supportive of me and has always done a lot, and he was the person who produced this department with the focus and the interest it had, which was for me a very very fruitful environment to be in. I have always got on very well with Rodney, probably because we had complementary skills and areas of competence, so we were able to appreciate and help each other without competing .

PSH. The second question I have been asking everybody is whether you can single out a particular piece of work or area of work that you have been involved with that you feel particularly proud of, you feel, well yes I did make a contribution there.

AR. Well in many ways the Strachan and Read book would be the thing I would go for because I think to a certain extent we did succeed in defining an area of science and making the framework through which people saw that area. If you are asking about more research achievements then of course it

has to be the Waardenburg and the PAX3. I mean we were very very lucky that it was such an interesting gene when we finally got there, but there is no doubt that's the one thing of significance, of real scientific significance. In terms of clinical significance, although I was only a small part of it, I suppose the vitamin trials have been the thing that has actually made the most difference to the lives of patients.

PSH. But if you had to choose one, I sense that your book was perhaps the most special to yourself in terms of . . .

AR. Well that's exactly it, because if we hadn't discovered PAX3 someone else would have, and the vitamin trials would have gone on without me, whereas the book, it was obviously Tom and me, that really was our thing, and as you were saying, nobody had actually got around to writing such a book before and nobody's really written one after, so I think that probably my part of it is my thing.

PSH. Andrew thank you very much, but just before I switch the machine off is there any major topic that you think I left out that ought to be recorded or do you think we covered most of the principal areas? These aren't meant to be exhaustive.

AR. We've not looked at the future of the science have we?

PSH. No, maybe I should switch the machine off, then we can chat about that a bit. Thank you very much.

End of recording.