Grant Sutherland

Personal Details	
Name	Grant Sutherland
Dates	Born 02/06/1945
Place of Birth	Australia (Bairnsdale)
Main work places	Adelaide
Principal field of work	Human cytogenetics
Short biography	See below

Interview	
Recorded interview made	Yes
Interviewer	Peter Harper
Date of Interview	07/08/2006
Edited transcript available	See below

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

Biography

Grant Sutherland was born in Bairnsdale, Australia on 2 June 1945. He is a graduate of the Universities of Melbourne and Edinburgh. He is Emeritus Geneticist at the Women's and Children's Hospital Adelaide, and an Affiliate Professor of the University of Adelaide. He has published two books and more than 480 papers. His major work has been the cytogenetic and molecular characterization of fragile sites on chromosomes including the fragile X. He is a past President of the Human Genetics Society of Australasia and the Human Genome Organisation (HUGO). He is a Fellow of the Australian Academy of Science and of the Royal Society of London and an Honorary Fellow of the Royal College of Pathologists of Australasia. He is a Companion of the Order of Australia (AC).

INTERVIEW WITH Professor Grant Sutherland, 7Th AUGUST 2006

PSH. It is 7th August 2006 and I'm interviewing Professor Grant Sutherland in Brisbane, Australia. Grant, can I start at the beginning and ask, what part of Australia were you born and brought up?

GS. I was born in Bairnsdale, which is on the coast of Victoria. At the age of about 12 the family moved to the outskirts of a town called Numurkah where my father moved onto a soldier settlement farm. He had been a soldier in the Second World War and this was a scheme to develop the country to some extent and also to do something for a lot of ex-servicemen who were either unemployed or under- employed. He'd been a market gardener in Bairnsdale before we moved onto the dairy farm. I completed my secondary schooling at Numurkah High School and left home at the age of 17 to go to Melbourne University where I did a Science Degree. I was not a particularly outstanding undergraduate student to say the least. It took me 4 years to complete a 3 year degree, failing 2nd year chemistry.

PSH. So did you come from any kind of scientific background at all? Was there anybody who was scientific in either of your parents or . . .

GS. No, there was no scientific background at all. As I say, my father was essentially a farmer and my mother had been a dressmaker prior to the war and during the war and then she just worked at home, home duties from that time onwards.

PSH. And what got you interested in genetics in the first place?

GS. Oh, that's a good question. I think it was probably breeding budgerigars as a teenager. In fact I'm quite sure it was. One of my secondary school teachers, Simon Rattray-Wood, was a budgerigar aficionado and I was breeding budgerigars and I went to a couple of talks that he gave to the local budgerigar society on the genetics of colour and feather patterns in budgerigars. And that seemed mildly interesting. And then I went on to University and genetics was first offered as of a half subject in the second year of the science degree and I found that quite fascinating. Michael White was the Professor there and he was a very stimulating sort of individual and developed my interest. So I eventually graduated with a major in genetics and then a sub major in zoology. I had gone through University with a view to becoming a schoolteacher, and if I can just digress for a bit, at the beginning of the third year of the Science degree, schools started a few weeks before the University started, that was the typical academic year. I had what was called a secondary studentship that paid our fees and gave us a living allowance, otherwise I would never have got to university and so they sent us out to schools for that couple of weeks and that finished me as a schoolteacher. For two reasons. Teaching I didn't mind. That was OK. People spent a lot of time yelling at children for running in corridors, not having the right sort of shoes and so on and I've always been a bit of an

anarchist anyway, so that I didn't cope with that at all. Then amongst the teachers there seemed to be two classes. There were those who were fully qualified with degrees who grumbled about the fact that they were trapped in the teaching profession. They could never get out. They would never be able to do anything else. They were underpaid and wasn't life dreadful. And then the other group of teachers were those that hadn't finished any formal qualification, because at that stage there was a real shortage of teachers and anyone who had perhaps one or two first year university subjects and had dropped out of a degree could become a teacher. These people were unhappy because, "I'm a better teacher than him and just because he's got a degree he gets paid more than I do."

So that absolutely finished me for teaching and in University vacations I had worked with the CSIRO animal, not doing genetics at all but doing very basic technical work. The project that I was involved with there, right at the bottom end, was developing a vaccine for bovine pleuro-pneumonia which is due to an organism called *Mycoplasma mycoides* and this was thought to be present in some of the Northern Australian beef cattle and there was a real determination to get rid of it. So as soon as I graduated, I chucked in the studentship and said I wasn't coming back. I wasn't going to be a teacher. And I thought I would keep working with the CSIRO, they thought they might have had a job there. And that had been wishful thinking I think on the part of the fellow that was leading the group. So once the university vacation finished, I was unemployed.

I saw a job advertised in something called the chromosome Laboratory of the Mental Health Authority in Melbourne, this was a small, two- person chromosome lab that had been going, and we are now talking the beginning of 1967, for 3 or 4 years, run by a fellow by the name of Saul Wiener who was a senior physician, allergist, who had done a sabbatical in the States just as chromosomes were coming on stream and he thought he would come back to Melbourne and set this up. And he set it up and they'd had a series of young women, he had two sessions a week or something like that, who had all come in, stayed for about a year and then either got pregnant or left for some other reason. So when this job was advertised I think I was the only male applicant and that was ample qualification at that time because they decided that they had not had a good experience with young women. So I got that job and I started to learn the technology of looking at human chromosomes, doing lymphocyte cultures and so on. I must say that I was largely self taught, which was not a good position to be in. Although Michael White had taught us some cytogenetics as part of the University course, it had been on grasshoppers, but at least I knew what a chromosome was. I didn't quite really know what metaphase chromosomes were because he looked at grasshopper chromosomes during meiosis, because he could do direct testicular smears and squashes.

PSH. Was anybody else doing human chromosomes in Australia at that time?

GS. Yes. There was a laboratory at the Royal Children's Hospital in Melbourne run by a woman by the name of Margaret Fitzgerald who I got to know a little bit, and who subsequently died. She had a very short career in

cytogenetics. Margaret Garson was doing cancer cytogenetics at St Vincent's Hospital in Melbourne. Margaret retired a few years ago after an illustrious career. Gillian Turner's husband, Brian Turner, had started a cytogenetics laboratory in Sydney. These all were set up around 1960 or the very early sixties just really, I guess, after the Moorhead paper showed that you could actually get chromosomes in a reasonably reproducible way from lymphocyte cultures.

PSH. About this time, you had some early papers, which the first ones seem to be cytogenetics case reports. Did they come out from your experience at that time?

GS. Ah yes. Almost anything you found was unique at that stage. You could publish literally an unbalanced translocation. You had no idea where the extra piece of chromosome material was from. I had a lot to do with a very skilful dysmorphologist by the name of Joanna Chakanovskis. She was Lithuanian I think and had come to Australia post war and talked about being in general practice in Lithuania and having to carry a gun when she went on rounds. But she had a wonderful knowledge of anatomy. She could describe an unusual face in paragraph after paragraph, detailing every physical abnormality. She had the name of everything; an average GP would say what? She taught me a lot of dysmorphology, not that I would ever claim expertise in dysmorphology.

PSH. But it meant you had material to work on that had a higher chance of showing something than the average out-of-the-blue, so to speak.

GS. That's right, because most of our patient population came from the Mental Deficiency Services and Institutions who had not really been looked at in any detail. It was also the time when the first publications on XYY and XXYY males in prisons came out, and I teamed up with a forensic psychiatrist by the name of Alan Bartholomew and he got quite keen on this and we studied a lot of prison populations, straight prison populations, we initially studied the tall inmates. We then did other populations both for the criminally insane and the just sheer criminal, and got quite a number of publications out of that because that was all relatively new, it wasn't first ranking but it was certainly in the second rank of what was being done then. As part of that we discovered that the hospital gardener was an XYY male. He was a slightly odd fellow, but he had never been in jail and as far as we knew, had committed no offences. He was the subject of a letter to the Lancet as a normal XYY male and was one of the very early so-called normal ones that had ever been found.

PSH. Did you establish links with the Edinburgh folk at that time, because you then went to Edinburgh for a spell didn't you?

GS. I went to Edinburgh, yes. I saw a job advertised in Nature for a cytogeneticist at the Royal Hospital for Sick Children. I had been working at this laboratory in Melbourne for about 4, 4½ years and as I mentioned earlier, I was largely self taught and I was running out of things to teach myself at that stage and so it was important to me that I move because I was stagnating. And I saw this advertisement and I applied and I was actually at the Royal

Children's Hospital, visiting Margaret Fitzgerald talking about cytogenetics. The phone went and she said "It's for you". I thought that's a bit odd. And on the other end was Douglas Bain calling from Edinburgh. Now this was, to a young fellow, pretty impressive at a time when I had to get the permission from the Medical Superintendent to make a phone call from Melbourne to Sydney. And it was at a time when international phone calls were almost unheard of, at least in the environment that I existed in, and he sounded keen, and would I come, so yes I said would. I arrived in Edinburgh at the very end of 1971 and so at that stage I had 4 to 5 years of experience in cytogenetics. I knew the literature, because there wasn't very much of it at that stage and I think I had read just about everything that had been published in human cytogenetics. The pathology department as it was at Sick Kids had a very good tissue culture laboratory and had a lot of tissue culture going on both for early inborn errors of metabolism studies and for cytogenetics. It was at the beginning of prenatal diagnosis, so I was able to use the prenatal diagnostic work for a PhD, almost as an aside, and I'm still slightly proud of the fact that I submitted my PhD 30 months to the day after I arrived in Edinburgh. Things have changed a little bit now but that was the time in Australia where the 4 year PhD was a quick one and the 8 year one seemed a bit slow. That all worked out very well. Douglas Bain was a rather sad character in some ways in that he was an alcoholic, although he wasn't too bad when I was there. He wasn't drinking during working hours. When I subsequently visited there a couple of times later on, he was. So that was kind of sad, but Douglas was very enthusiastic about genetics. He taught me a lot, particularly more in the dysmorphology area. I attended a lot of autopsies of malformed children that he carried out, and really started getting a feel for dysmorphology and the role of genetics.

PSH. Did you meet up with David Brock at that point?

GS. Oh yes.

PSH. I noticed again quite a few of the papers you wrote from Edinburgh were joint ones with him.

GS. That's right. There was an interesting observation that I made in that we'd got an amniotic fluid from a fetus which was subsequently shown to have anencephaly; ultrasound wasn't that flash in those days, so some of these things weren't picked up on ultrasound, not in a prior way; it could often be seen when you knew the diagnosis. And David was working on his alpha-fetoprotein at that time in particular and so we worked out that this fetus had anencephaly, and the interesting thing about it was that the fluid was full of rapidly adherent cells which in retrospect I showed were macrophages; and that looked for a little while as though it may have been an additional diagnostic for open neural tube defects. It panned out to be notoriously unreliable but it meant that I did make that connection with David and we were working on that together for a little while.

PSH. So when you went back from Edinburgh, did you go back to Melbourne or did you move to Adelaide at that point?

GS. No I moved straight back to Adelaide. I had applied for the job that I eventually took in Adelaide, before I went to Edinburgh. I had looked at it then and there were a few reasons why I didn't take it. I didn't think I was going to learn any more there than I knew from Melbourne, because there was no senior figure about that I thought was going to be able to teach me very much, and I had a house in Melbourne that was going to be a bit difficult to sell in the state it was in. So I didn't take that job but the Pathologist who tried to recruit me, a fellow by the name of Rodney Carter, then more or less followed my career and once I had my PhD, was quite keen for me to come back to Adelaide. So I came directly back from Edinburgh to Adelaide. In fact I've never been a post doc.

PSH. So when you went back to Adelaide, was this a new unit or did this have a bit of something there already in terms of cytogenetics?

GS. No, it had a reasonable history. Some early cytogenetics, and I guess this is another one of the sort of things that was happening in Australia, started in the very early 1960s, in the University of Adelaide Department of Genetics, by a reasonably well-known insect cytogeneticist, by the name of David Hayman, who had done some cytogenetics there in collaboration with the local hospital and then a technical cytogenetics unit had been set up under the auspices of Rodney Carter as the pathologist and there were 4 technical staff there who were running this when I arrived. So he said right, here's your unit. You've got 4 people and at least half of the time that they've got can be used for research

PSH. That's quite a good starting point.

GS. It was marvellous, and it wouldn't happen in today's healthcare system.

PSH. So Grant, when did you first encounter Fragile X?

GS. Let me answer that slightly indirectly. I had these resources for research and I really didn't know what I was going to do. I had been doing work on amniotic fluid cell culture for my PhD but that was now pretty much becoming a routine service thing. And so I looked around the unit and there were a number of patients that had been studied previously there, who had fragile sites on their chromosomes. No Fragile X , these were all autosomal fragile sites, and so I thought I can re-study a couple of these and it will give me something to do while I think of something worthwhile to do. These patients were all mentally retarded, that was an ascertainment problem, not a consequential one. So it was just a matter of ringing up the local institution and saying can I have a blood from him, him and her please. Things that with today's ethical environment I would never ever be able to do and if I can have another little aside, I have a bee in my bonnet about ethics, not that I am unethical, but the whole concept of committees and so on rather than the good old do-no-harm precept, run it past a colleague, think of the experiment in the morning and do it in the afternoon. That fun and immediacy has gone from science, when you are working in the human area or the animal area and I think that is a really sad thing, particularly for young people coming through. I mean you just get weighted down with bureaucracy and by the time you get

an approval you have probably forgotten why you wanted to do the experiment in the first place.

Anyway with that off my chest . . . So I got the blood samples in and set them up - no fragile sites. I got out the old slides at the place of storage and yes, they were there. So I had a problem. Fragile sites have been good to me. So after playing around with these for a while and not really getting anywhere, I went back to visit the old laboratory where I'd worked in Melbourne, talked to the, now female, who was the cytogeneticist there, a lass by the name of Jill Harvey and she showed me eight Fragile X families that they had found. She was working with a psychiatrist by the name of Cliff Judge. Now Cliff I had known quite well when I was working there myself and he worked in the area of mental deficiency, mainly in routine care of institutionalised mentally retarded patients. And he had seen Herb Lubs' original publication on Fragile X and apparently on his copy he had written 'we must have some of these' and so they had this collection of families and that paper was published in 1977; Harvey, Judge and Wiener, were the authors and that was the first paper that got Fragile X off the ground as an entity associated with X-linked mental retardation. Herb Lubs' paper had been, not forgotten, but nobody else found very much. There had been, one or two cases in the French literature and then talking to other people around the track, one or two said 'I think we saw one', but nobody had done anything with them until that paper came out. So I looked at them and I thought, this is one of those Fragile sites. It's the same as I've been looking at on the autosomes, I didn't know what I was doing wrong. I could not figure it out. So I thought I'll do everything that I used to do there. Absolutely everything. That lab was still using medium 199, which was the old Model T Ford of tissue culture media, and the lab I was in in Adelaide had changed a while before that to either Ham's F10 or RPMI, the more modern culture media. So I got some more blood samples. It was very easy, just ring up and yes the Fragile sites were there in medium 199. And so we did a few confirmatory experiments and repeat it and then I got a Fragile X family from Adelaide, well an X-linked mental retardation family that I showed had the Fragile X and I could see it in medium 199 and not in the other media. That relatively small amount of work got me a paper in Science in 1977 and that's what started the whole thing.

Then I kept working on it and trying to figure out what's in 199 that's not in the other culture media. And medium 199 has got a long and complex recipe, a list of ingredients, much longer than the more modern culture media. It's got alcohol in it, it's got detergent in it, it's got some nucleotides in it, it's got all manner of things in it and I was quite convinced that it must have been one of these things that was causing the fragile sites to appear. The Commonwealth Serum Laboratory in Melbourne made up a few batches of media for me where they'd left out one or more of these ingredients, but nothing ever happened and I used to literally take out these recipes, look at them and scratch my head and say what is the difference. And purely by chance I spotted one day that there was virtually no folic acid, or very little folic acid in medium 199. It's got .01 mg per litre or something like that, a very tiny amount, and there was about 40 or 50 times that amount in the others, and so it is an easy experiment to add something back into a culture medium, and so I did it and the fragile sites went away. And I can still remember that day when I looked down and 'a quick look at the slides, nothing there, another

one, get out the controls and yes they are there'. And that was an incredible feeling. You don't make a lot of absolute total discoveries in science, or at least I haven't. So that really set a path and I guess my career and fragile sites have gone in parallel ever since then, when that work got me two very substantial papers published back-to-back in the American Journal of Human Genetics in 1979 and the first of those has been cited almost 500 times now. It's not all self self-citation.

PSH. What year was the first edition of your book on fragile sites?

GS. Right, let me backtrack a little bit again. When I published those two papers in the American Journal of Human Genetics, Fred Hecht wrote an editorial covering them and that started a bit of correspondence between us, and I went and spent a three months sabbatical with Fred and Barbara Hecht in Phoenix in 1983, and the book on fragile sites was essentially written during that time. I had a bit of tidying up to do once I got back but Fred was very good. He was very entrepreneurial about the whole thing and I won't say that he contributed a lot of the actual meat to it though he was very good at reading what I had done and saying "Hey, what about this". He did make a real contribution to it, he provided the environment and the entrepreneurial flair to write a book, and that appeared in 1985. We toyed with a second edition the early nineties. But things had widened out tremendously by then. Fragile X had been cloned. A repeat expansion, as you know so well, had been found in myotonic dystrophy, in Huntington's disease and so on, and so the whole area, which was something where I literally was still reading every paper from beginning to end, had now got to a stage where you didn't quite read every paper from beginning to end because the literature had just burgeoned, and so a focus for a second edition of a book just on fragile sites didn't seem as though it would have worked, and the whole field was then progressing so rapidly that anything published at that point would have got out of date very quickly. So the second edition never eventuated.

PSH. When was it you started getting involved with molecular techniques in the lab?

GS. That would have been around 1981/1982. I'd concluded that I wasn't going to learn any more about fragile sites from cytogenetic manipulations. We had done everything imaginable in altering culture conditions, media formulas and so on and we really were not learning anything new. So it seemed to me that the only way I was ever going to understand what a fragile site was, was to look at the DNA in that area and I hired a research assistant, mis-using grant money that had been intended for something else, who had just finished an honours degree in molecular biology and I don't know that he ever actually ever got a Southern blot to work. Then I got a post doc who was a pharmacologist who had spent about 6 months at NIH, and had done some molecular work and I think after a while she managed to get a Southern blot to work, because that was the technology. This was pre PCR and so we started eventually hunting, not just the Fragile X. That was something that I thought was going to be too hard. We were looking at chromosome 16, primarily because it had a folate sensitive fragile site which is the same sort of fragile site as the Fragile X. Most of the fragile sites on human chromosomes are the common ones in which I was never very interested, then there are the

rare ones, and most of the rare ones are same as the Fragile X to all intents and purposes, when you study them at a tissue culture/ cytogenetics level. The same conditions are required and I was quite sure, and I still am, that they would all have had the same molecular mechanism.

So chromosome 16 seemed to be a good place to start for variety of reasons. It had one of the folate sensitive ones on the short arm and one of the folate insensitive ones on the long arm. The chromosome can be selected in tissue culture because it's got a gene, APRT, on the end of the long arm. One of the senior people working with me was David Callen who was very good at doing cell fusions and selecting for chromosome markers in them. So what we were doing, because there were no maps or anything, of course, as you know, were really starting from scratch. So we made a panel of about 90 different cell lines with different parts of chromosome 16 we generated from naturally occurring rearrangements of chromosome 16 which we had scoured the world for, and we put these into hybrids and then selected for the component of the translocation the APRT gene on was on. So we could map things into about 90 intervals on chromosome 16 and we were using this to try and make a better map to be able to get us in to the fragile sites. We were developing in situ hybridisation so we could map things relative to a fragile site, so if you had a bit of cloned DNA, we could see which side it was on and we were trying to get closer and closer .

It was going well actually because it was the early days of the genome project. The Los Alamos lab had chosen chromosome 16 as the first chromosome it was going to do and as soon as we heard that we thought we were dead in the water. The resources they've got and what we've got, it will never work and we will be swamped, but it worked out very well. They funded us for a few years and so that increased our resources. But then the X came along, people started making hybrids that we could access. We had an X 16 translocation with break points in the right places, not at the fragile site, just above it, and so we thought look, we can get this into a hybrid, we can then just randomly clone bits of DNA and map them back and so we did that. We had an Irish post doc by the name of Val Hyland. Val now runs one of the diagnostic molecular labs here in Brisbane and he made a number of well-mapped and cloned bits of DNA on the end of the X chromosome. One of those actually contained the Fragile X but we didn't know that for quite a while. So we were working on other clones around the area. The YAC technology had come along. We had big bits of DNA. We were mapping them.

We were collaborating with the other groups, particularly Steve Warren who had made a lot of hybrids with breaks that he thought were at the fragile site. One or two of them probably were but the rest of them were in the general area. They were useful reagents and with Jean Louis Mandel, who was also cloning bits of the end of the X chromosome and making maps. I had a fairly big group by this stage and I was trying to get people to work on a particular YAC that I thought it had to be the main chance but no. It just didn't seem to behave properly, so they wanted to work on others. Eventually I persuaded people to have a look at this one and then we mapped on to it a couple of Jean Louis Mandel's probes that he thought were on either side of the fragile site. And so I thought oh, we've got it now, but we had terrible trouble with

that YAC. It just didn't . . . we couldn't map it. We didn't know a lot about YACs but we knew they were rod shaped chromosomes, but this was a circle. And so nothing mapped and the lass that has taken over my job in Adelaide now, Sui Yu, was a PhD student, and she twigged one day that if it was a circle the map all fitted. So we went from that, sub-cloning the YAC down to smaller bits and using in situ hybridisation we were able to get in there and then we finally got it, they showed me a Southern blot, with this thing moving all over the place and we thought "What the hell's going on here?"

PSH. Because at that stage, nobody had any idea about DNA instability

GS. No.

PSH. being a possible cause.

GS. No, there had been talk about it might be an amplified sequence or something like that, but the whole concept that this sequence was going to change from generation to generation was, in fact it was really anathema to genetic dogma that we had a stable genome. I think we know a lot more now that genomes aren't as stable as we thought they were, but you know this was just anathema really.

PSH. What made you realise that it was just an unstable sequence?

GS. We had a pretty reasonable map by this stage and we could follow it through families and everything else seemed fine. By this stage the collaborating groups were all sort of dashing for the goal independently.

PSH. I was going to ask that Grant, because we both had very similar experiences. You have collaborations which fluctuate and then there comes a point where there is a very clear end point and as you said, everybody rushes for it and sometimes things work out with credit spread around in a reasonable fashion and sometimes they don't, but I've always felt that for myotonic dystrophy and I had the feeling for Fragile X also, perhaps more by luck more than judgement, the main players all ended up with a reasonable chunk of the credit. Do you feel that's a fair statement?

GS. At the time, we felt a little bit annoyed because we had submitted our paper to Science and it had been accepted and then Jean Louis Mandel submitted his and they held ours back so they could put them both in the same edition, as the journals do. And so we felt a bit miffed about that but in retrospect it was fine. The other grouping which had been Steve Warren, Tom Caskey and Ben Oostra had formed their own little consortium at that point, and I'm not sure what day of the week Science comes out, say it's Tuesday. Well I think on Friday, Cell came out with their paper on it. So the three groups did well. Kay Davies had been working pretty intensively on it and missed out badly I think. She had a little bit of stuff coming out with Fragile XE. But she missed out on anything to do with Fragile X. She hadn't really been part of the collaboration that had been going on, but it wasn't a formal collaboration. It was a 'you show me yours, I'll show you mine' sort of thing on odd bits of data and odd reagents were exchanged. I think in

retrospect it was a good outcome. The science got done. The patients got helped and everybody got a slice of the action.

PSH. At what point did you realise that this might be not just one isolated example of this but might be relevant to other conditions like myotonic and Huntington's, because things happened very fast didn't they?

GS. Is that a loaded question Peter? Is that a Dorothy Dixer?

PSH. No.

GS. I'll tell you why I said that. I thought that immediately I saw what was going on in Fragile X, I just said to myself, here's an answer to anticipation.

PSH. I remember you wrote a little letter to the Lancet.

GS. That's right and I sent you a copy when I submitted it to the Lancet and said Peter, if they knock this back do you think you could put it in the Journal of Medical Genetics.

PSH. I'd forgotten that. But they didn't.

GS. They didn't knock it back so I didn't need to bother you again.

PSH. Yes. Well, that was very relevant. So coming back to this anticipation. Had anticipation been widely talked around in the Fragile X community?

GS. Not really. It had been talked about a little bit because of the so-called Sherman paradox. But this wasn't seen quite as anticipation because anticipation had always gone back to age of onset rather than differential penetrance.

PSH. And it had always been in autosomal dominant conditions.

GS. Yes and primarily myotonic dystrophy.

PSH. Exactly.

GS. Although there were sort of little hints of it in other areas.

PSH. So what put you on to anticipation? Had you been taking a lateral interest in the other conditions or was it just something that had been in your mind and you had been wondering about?

GS. Oh no. I had always been interested in, I suppose genetic phenomenology. I think I might have written an undergraduate essay on that at one stage, so it was something that had been in my mind for a long time and in fact I think I remember at one stage having a conversation with you and asking you whether you thought it was a real phenomenon in myotonic dystrophy, because Penrose had demonstrated so elegantly that it was just ascertainment bias and nothing else At that stage, this was before we knew anything about mechanisms, you said you thought there was something in it.

PSH. That's interesting, and the reason I said that was because I had been closely involved with Chris Höweler who had been doing his thesis on myotonic dystrophy and anticipation. Now he had convinced me even though he hadn't convinced his colleagues. I was an external examiner on his thesis and his colleagues said "Oh he has done a very good study of myotonic dystrophy. Pity about his crazy ideas on anticipation, but he deserves the thesis even so." It's true, because I had looked laterally to Fragile X and decided well, there's something funny there. Like you, I didn't think it was exactly the same because it wasn't age of onset.

GS. That's right. But as soon as I saw a mechanism which allows something to change from generation to generation, and in Fragile X we knew about the non-penetrant, or the pre-mutations and so on and I thought, look this could work in myotonic in the same way. And was most gratified when almost, it was only a few months later, it was shown to be.

PSH. It was, I think 6 months later, it was in the February to March and again, very interestingly in that series of collaborations, again everybody ended up with a reasonable piece of it. Again probably more by luck than judgement, as these things go. Now once Fragile X had been cloned, did you find that you felt, well, time for a change, or did you feel really that was going to produce another wave along the same lines?

GS. We lost our way a little bit, because there was a feeling of anti-climax I suppose. I and the people who were in my group didn't have a good feel for the functional type of stuff that we should have done after that and others did that much better than we did. Ben Oostra made his mouse, there was a lot of work on the protein, so we rather missed the boat there. Largely I just did not have the background as a biochemist to start saying, right this is the way we go. We stuck with what we knew and we went back to chromosome 16. We got both the fragile sites on chromosome 16 that we had been looking for. The folate sensitive one has the same mechanism as Fragile X, the CCG repeat that amplifies. The folate insensitive one is a different sort of repeat and then we went on to chromosome 10, where there's a different sort of folate insensitive site, but it's also a repeat expansion. It's a slightly variable approximately 42 base pair and VNTR type of thing. We did some work with Fragile XE and Fragile XF and at that stage we ran out of puff a bit.

PSH. Interestingly I think all the groups involved in this area, indeed in gene cloning generally, hit the same difficulties, because the commonality of technique with DNA work was very great and you could use the same techniques for almost anything, and then the moment a gene came out it might be any kind of protein, and everybody was almost sent back to the starting point, weren't they?

GS. That's right.

PSH. So it was quite democratic in some ways because it hit everyone. It was a difficult time. So, where would you feel, where did you invest most of your interest in those next years after Fragile X came out?

GS. In getting other fragile sites. I guess I'd always had that interest in the whole fragile site picture rather than just Fragile X. Fragile X was what gave it a profile, made it fundable because at least one of these things was clinically relevant. So I was keen to go more into fragile sites and try and build up a more complete picture of what fragile sites are rather than just saying here's Fragile X, we've got it now. Let's run with that one. Apart from our difficulty with the background technology and the need to do something completely different. And that worked quite well, I mean the folate sensitive one on 16 was the Science paper. The insensitive one was the Cell paper, the next one was a Molecular Cell paper and then, a couple of years ago now, we collaborated with a group in Germany and got one of the folate sensitive ones on chromosome 10, and that was a Genomics paper so things were going down. But the group changed; Joseph Gecz joined the group. Joseph is outstanding. He found the gene that runs off Fragile XE and the one that runs off Fragile XF but his primary interest is X-linked mental retardation and he has taken his area of things in that direction.
In the mid nineties I had a call from a neurologist in Melbourne by the name of Sam Berkovic, who you may know of, and Sam's passion is epilepsy and he wanted us to get involved in epilepsy genetics. I was quite keen to do that because I didn't really want us to start moving into rarer and more esoteric things as we went, and so something that was moderately common was good. I mean as a problem each individual cause could be hideously rare, but overall I thought it was worth tackling. Sam was a clinician who was painstaking in his phenotyping. The lab would get calls every day from somebody who wants you to do something. You might get two blood samples, probably from patients with different conditions anyway and then they'll lose interest. Here was a guy with a passion and so we moved into epilepsy genetics and John Mulley led that area. I suppose to some extent I had always had almost a policy of trying to make the whole group function such that if I got run over by a bus, they would come to the funeral and then they'd get back to work the next day and not notice I had gone, and I eventually promoted myself to total irrelevance.

PSH. Can I ask you, your second book, when did you first link with Mac Gardener?

GS. Oh right. I'd known Mac for a long time, as a clinical geneticist who worked in New Zealand. He then came to the Murdoch in Melbourne and got in touch with me at one stage and said 'Look I want to do a book on Genetic Counselling and I'm having a bit of trouble with the Fragile X chapter. Would you like to do the Fragile X chapter?' And I said yes, I could probably cope with that. And then there were other bits 'would you just have a look at what I've written here?' And so it became a good collaboration. I mean Mac has done the lion's share of it, absolutely no doubt about that, but that has been very pleasing. The book has gone reasonably well. There will be, provided everybody delivers, another edition with Lisa Shaffer as the lead author.

PSH. Good.

GS. Mac will be the back-up and I might read the proofs, if I'm still around when it happens.

PSH. The other person you must have really had a lot of contact with over the years is of course Eric Haan. I mean, I have known Eric a long time too and I have always been amazed how he kept the clinical side going through quite lean years really before he eventually got good support.

GS. Yes, I have had a lot to do with Eric. I was on the selection panel, that got him into the hospital and it was interesting. I don't think I'm breaching any confidences to say that one of his referees was David Danks, and David's reference went: 'This was the best medical student I have ever encountered. This was the best RMO I have ever seen. This was the best registrar that has ever been through the hospital, the best trainee I have ever had. I am going to do everything I can to keep him in Melbourne."

PSH. That sounds fairly typical for David.

GS. Eric has been a real godsend to the place; to the extent that I can judge he's a very good clinician, a very good clinical geneticist. He has a real empathy with people and gets on very well with them. He's got very good political antennae and operates well at the higher levels. He's done very well here, and now, I don't know whether you are aware, he is Head of all of genetics in the Women's and Children's Hospital. The department which now contains my old department and what used to be chemical pathology and clinical genetics is now called Genetic Medicine. Eric is the Head of it and that happened about three years ago.

PSH. That's good. I must finish soon, very soon Grant, but I have been asking everybody I have seen, two questions. The first is, is there any particular piece of work which you look on with special, what you might call, affection, or feel that this was a really special contribution you made. If you had to just choose one, what would you settle on?

GS. I think it would be the discovery of the culture medium that you needed to use to see fragile sites. For a variety of reasons; one, I did it all myself. I had some technical people who used to score slides for me. Although I did a lot of that myself as well but I got the patients, I set up the cultures. I did all the pre-testing to make sure everything would work. All of that I did, and it then opened the way until the Fragile X was cloned as a diagnostic method for Fragile X syndrome. So to me, it had a lot of personal satisfaction because I had done it all myself rather than leading a team of people and then secondly, it had a particularly useful outcome. So I think that's probably about it.

PSH. It's interesting that most people when I have asked that question have given a very comparable answer. The feeling that this was something you really did yourself is something that stays with people through their lives. The other thing I've been asking is, is there any single person who you feel was particularly important in developing your scientific progress and career or was it spread over a number of people?

GS. I don't think I have ever had a real mentor as such. I had people that helped me for periods. Douglas Bain as a PhD supervisor. I mean the main people are the ones that have worked with me - Elizabeth Baker. I don't know whether you know Elizabeth Baker?

PSH. I've never met her.

GS. She was with me for about 20 years and she started off doing as I asked her. She eventually became my eyes, my ears and I think, three quarters of my brain. And so she was somebody that I could rely on totally. She actually did quite a lot of stuff that I got credit for. In fact I used to introduce her as this is the person who does the work that I get the credit for.

PSH. Is there anything else large, in terms of a phase of your life or your work, that I've not asked about Grant, that you feel I ought to kind of record?

GS. I think you've been pretty comprehensive.

PSH. In that case I will say thank you and turn the machine off. Thanks very much indeed.

GS. It's been a pleasure.

End of recording.

Postscript
GS would like to acknowledge that many people have contributed to the work described in this interview. Only a few of them have been mentioned by name in it. The others who made important contributions are too numerous to name individually but their names can be found on the many publications from the group.