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VIDEO INTERVIEW TRANSCRIPT

Ferguson-Smith, Malcolm: transcript of a video interview (06-Jun-2015)

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Ferguson-Smith, Malcolm: transcript of a video interview (06-Jun-2015)*

Biography: Professor Malcolm Ferguson-Smith (b. 1931) is Emeritus Professor of Pathology, University of Cambridge. He graduated in medicine at Glasgow University in 1955 and, while undertaking postgraduate training there in pathology, was introduced to research on sex chromatin under Bernard Lennox. An interest in Klinefelter's syndrome in 1957 to 1958 led to his appointment as Fellow in Medicine at Johns Hopkins University, Baltimore, in 1959, where he established the first chromosome diagnostic service in the USA, and undertook cytogenetic research into Turner syndrome. Research interests include molecular cytogenetics, karyotype evolution, vertebrate sex determination and comparative genomics. He is joint author of *Essential Medical Genetics*.

[1]. FROM MEDICINE TO GENETICS: KLINEFELTER'S SYNDROME

Well, it was really by accident, because when I graduated from medicine and had done my internships, I decided that the best thing to do, to train for being a general physician in medicine, and I was an internist, I had better learn something about the science of medicine. So I decided that to spend some time in pathology would be a good idea. So of course I went into pathology with the idea of training for general medicine. And while I was there, one of my teachers in the Department, a man called Bernard Lennox, who was a very great character, he invited me to join in his research. And so he wasn't, he told me I wasn't doing very much of interest, and I might as well come and help him. In actual fact we were all working very, very hard at training in pathology, but I was very glad to come and work with him. So what we did was we looked at - he had decided that the best way of studying individuals with paradoxical sex anomalies would be to use the buccal smear as a screening tool to search for patients with Klinefelter's syndrome. So my job was to make buccal smears of, first of all, children with undescended testes, and then, when we didn't find any Klinefelter's syndrome among the children with undescended testes, I said, 'Oh, well I know that Klinefelter's syndrome is associated with infertility, so why don't I go to the infertility clinic?' And so I went to screen patients in the infertility clinic, and the eighth patient I found was a patient with Klinefelter's syndrome. So, to cut a very long story short, I found that about 11% of the males in this infertility clinic with severe infertility problems had Klinefelter's syndrome, okay? And as some of these males had learning difficulties, some of them had been at special schools, I thought, 'Perhaps if learning difficulties might be a part of this syndrome, so perhaps we should screen in children with learning difficulties?' And we screened both children and adults with learning difficulties using this buccal smear test. And the result was 1% of the males that we screened had this same condition and, of course, afterwards we learned that Klinefelter's syndrome was quite common; it was between 1 in 500 and 1 in 700 of the general population, but this was a definite increase in frequency among those with a handicap. And one of - I'm sorry this is so long a story, but the story is quite good - so one of these patients turned out to have spermatogenesis and I should explain that the urologist who was in charge of the infertility clinic, part of his workup for the infertility male patients was to do a testicular biopsy. And as I was in the Pathology Department I had access to all the testicular biopsies from these patients, so I did a general review of these, first of all of these testicular biopsies, and found a great deal more patients with Klinefelter's syndrome among them. And that was, it interested me greatly.

* Interview conducted by Ms Emma M. Jones, for the History of Modern Biomedicine Research Group, 06 June 2015, in Glasgow. Transcribed by Mrs Debra Gee, and edited by Professor Tilli Tansey and Mr Alan Yabsley.

[2]. KLINEFELTER'S SYNDROME, CHROMOSOMES & VICTOR MCKUSICK

But one patient interested me particularly because he had in his testes, had a tubule that had full spermatogenesis. And patients with Klinefelter's syndrome are sterile, and don't have any spermatogenesis. And the fact that they had female sex chromatin meant that the prevailing view was that these individuals were sex reverse females. So in looking at the spermatogenesis in the testicular biopsy, I found this tubule in which there was sperm, but more important there were cells in which I could recognize the XY pair, the XY bivalent pair. So this man had a Y chromosome.

So I said, 'This is very interesting. Nobody knows about this.' So I went off to the Genetics Department and I said to Professor Pontecorvo, 'Please could somebody in your Department study the chromosomes of this man and find out whether in actual fact he has a Y chromosome?' because I didn't know anything about how to look at chromosomes. And he said, 'Oh, well we're not terribly interested in cytogenetics.' He referred me to his colleague who looked at the chromosomes of *Aspergillus*, and so Charles Elliot said to me that he really wasn't very interested, he didn't know anything about mammalian chromosomes, but he knew a chap who did. And so he put me in touch with a man called Charles Ford, and Charles Ford, this was in 1957, and in 1957 Charles Ford was just about to publish a method for looking at human chromosomes which involved taking a sample of the bone marrow. And Charles said to me, 'Well look, I haven't published the method yet, we're still working it out, Pat Jacobs is with me, we're working this together with a man called Dr Lazlo Lajtha,' who was a haematologist, hence the bone marrow. And 'So I'll let you know when the method is ready. But meanwhile what you can do is you can, if you've got any more of these interesting people, I've never heard of them before, we can, you can look, if you can take a little bit of bone marrow from them, you can look at the chromosomes yourself.' So he said, 'This is how you do it,' and so on. And so I tried, and every time my urologist friend, who was doing these biopsies, every time he did a biopsy on a Klinefelter patient, he gave me a little bit of tissue so that I could look at the chromosomes in the testes. And also allowed me, after permission of the patient of course, to make a little hole in the patient's sternum right here, and so I can remove with a syringe some bone marrow.

And my bone marrow preparations were terrible, were absolutely awful. I could see chromosome occasionally; I didn't know how to count them. One chromosome looked much the same as another and there was a lot of dust in the preparation, and it was really very difficult. So my Professor said to me that, 'Clearly you need time to do this, you can't, while you're training at pathology with us, you are busy doing post-mortems and looking at surgical biopsies and working hard to train to be a pathologist,' - although I wasn't going to be a pathologist - 'I'll see if I can find a place where you can have time to do this.' So, to cut a long story short, he knew somebody who knew somebody called Victor McKusick, who knew that Victor McKusick was recruiting medical specialists to form a new division of medical genetics in Johns Hopkins Hospital. Again, to cut a very long story short, it was in the summer of 1958, I was interviewed by Victor McKusick in Liverpool, in the Adelphi Hotel in Liverpool, and Victor was able to offer me a job immediately, said he'd like me to come and be a Fellow immediately. And I said, 'I'm sorry, we're working on these Klinefelter patients, I have to get my work published, but I hope to be finished by December.'

[3]. KLINEFELTER'S SYNDROME, BECOMING A MEDICAL GENETICIST IN THE USA & THE UK

So in January I set sail for Baltimore in the SS Carinthia and when I arrived in Baltimore, I arrived simultaneously with the publication of the result of Down syndrome from the French group. They found this extra chromosome in Down syndrome. So I arrived in America just at the time that everybody suddenly was presented with the fact there were abnormalities in chromosomes in certain individuals. And just shortly after that Pat Jacobs was able to do, was able to look at a patient with Klinefelter's syndrome and was able to show there was in fact Y chromosome there, it was two X's and a Y. So I felt, you know, this is great, this is what I said it would be, but I hadn't done it myself, and so I got into cytogenetics that way. So that's how I started in genetics. And of course I never went back into general medicine. I left, I left pathology several years later, and became a medical geneticist running both diagnostic laboratories, and also teaching

medical students and having, running a clinic in medical genetics and counselling women who had had abnormal children. And this fascinating, wonderful area, was something that I never, never left.

And my idea was that, at that time nobody believed that genetics had anything to do with medicine at all. Genetics played no part in medicine whatsoever. When I told my colleagues that I was going to go into medical genetics in the United Kingdom, they said, 'Why are you going to do that? There aren't any jobs. There are no jobs for you.' So you had to take a risk. And I took a risk and went into a subject where there were no jobs, and so I'm very glad I did.

[4]. USA: GENETIC DISORDERS & ABNORMAL CHROMOSOME DIAGNOSIS; TURNER SYNDROME

Well, I think the thing that I'm most proud of basically was being able to set up a system for providing the services to patients who had problems with genetic disorders and their children, and setting up a clinic to provide advice to individuals at risk, couples at risk of having an abnormal child about the risks in future, and what we might do about them. And, of course, also many, many people came along and said, 'Look, we have these abnormal children, could you please look at their chromosomes and see if you can find a diagnosis and abnormal chromosomes?' So quite a lot of our work was setting up a chromosome diagnostic service and providing these diagnoses for families who had abnormally, children with disabilities. So at that point, I should have said that in the United States, I set up the first cytogenetics, the first chromosome clinic, that was in 1959. I set up the first diagnostic clinic in the United States for chromosome abnormalities, and that meant that lots of patients were referred with chromosome abnormalities or potential chromosome abnormalities for diagnosis to our clinic.

And in Johns Hopkins Hospital where I was there was a wonderful paediatric endocrinologist called Dr Lawson Wilkins, and he was a pioneer in paediatric endocrinology. And he had a particular interest in children with ambiguous sexual development and so he referred his patients, he was happy to refer his patients, at least blood samples from his patients, to my little diagnostic lab to see if they had chromosome abnormalities. And with that material, I was able to collect many cases of patients with Turner syndrome and with ambiguous genitalia, in which it was possible to determine what type of chromosome abnormality, what type of particularly of X chromosome or Y chromosome abnormality they had. And out of that grew a research conclusion which was very valuable, which was that those patients that had lost a short arm of the X chromosome, developed the full-blown Turner syndrome with infertility, and short stature, and various malformations, and those that had lost the lower part of the X chromosome were not short in stature, were infertile but not short in stature, did not have the features of Turner syndrome. So from that we were able to come to the conclusion that the things that matter for Turner syndrome must be in the short arm of the X chromosome. And, of course, individuals that have, I should explain that most patients with Turner syndrome, as my audience would know, have a single X chromosome and no other chromosome. They don't have a Y chromosome and they don't have two X's, they have one X.

But individuals with full-blown Turner syndrome with only one X chromosome, were short in stature and had these multiple malformations. But I thought to myself, 'But males have only got one X chromosome and they don't have any of these features, so there must be something on the Y chromosome that stopped these individuals, that stopped males, from getting Turner syndrome.' And so my idea was that there were genes that were expressed on the X chromosome that had copies on the Y chromosome that had the same function; they were expressed on both the X and the Y chromosome and prevented Turner syndrome. Therefore Turner syndrome was due to haplo-insufficiency of genes on the X chromosome, and that mapped the Turner genes to the short arm of the chromosome X and its corresponding region on the Y chromosome. So that was a bit of science that came into it.

But when I came back to the United Kingdom, back to Glasgow in 1961, I was offered jobs in America at the time, but as I said I was going to come back to Glasgow when I left, and my idea was that I would try and introduce medical genetics to medical practice in Glasgow and that was my kind of aim, as well as doing some research, continuing the research that I was doing. So it's been a wonderful experience for me to see

the period change from where genetics played no part in medicine to where genetics is the actual basis of medicine, is the fundamental science that's underlying all of medicine. So that's been a wonderful journey for me, and I guess I'm very happy that I happen to be involved. But you asked me what were the most important things. I think the most important thing for me, because I was trained as a doctor, the most important thing for me was to actually, to be able to provide these services for people who needed them and I guess that's… I think that's probably the most important thing that I was involved in.

[5]. USA: CHROMOSOMES, LEVAN & HSU

You ask about obstacles that got in the way of my career. I suppose the first one was, the biggest obstacle was finding somebody to look at the chromosomes of these people that I wanted them to look at. Of course everybody was busy with their own work, and nobody wanted to be bothered with something they'd never heard about, so I had to realise at a very early age, if you really wanted to do something, if you want something done you have to get on and do it yourself. And the second obstacle was, well, once you made that decision, then there was the trouble of getting the technology working. And to be perfectly honest I didn't get the technology working until I met two important people in the United States, and one of them was a Swedish geneticist called Albert Levan, and Albert Levan was one of the two people who had discovered the correct chromosome number in man. They had shown that it was 46 and not 48. He worked with his junior colleague, Joe Hin Tjio, and Tjio and Levan discovered that humans had 46 chromosomes, and that was in 1956, okay? And I was now in 1959, and I was in Baltimore in the United States, and I was giving, had to give a lecture in Atlantic City to the physicians, the American Physicians meeting in Atlantic City, in the Steel Pier in Atlantic City. It was a memorable occasion because there were 5,000 people in the audience, 5,000 physicians and I was talking immediately after Albert Sabin, who was talking about his vaccine for polio. So of course everybody came to listen to Albert Sabin, and fortunately they didn't get up when I came next. So they had to listen to this Scottish boy telling them about the new discoveries in Klinefelter's syndrome. And I guess that was an exciting time for me, but at the time, at that time, I met Dr Hsu, who was a cytogeneticist who worked at Houston and he invited me down to - I told him my problems about how I was hopeless at making chromosomes - so he invited me down to Houston and to see what they did. And in fact at the same meeting I was invited to give the same talk as I'd given in Atlantic City to somebody in the Baylor College of Medicine. So I said, 'Oh, I'm going to come down to Houston anyway, can I come in and spend a few days with you?'

So that was the most important two days in my, up to that time, because both Levan and Hsu showed me how to make cell cultures and how to make chromosome preparations, and Albert Levan showed me how to draw pictures of chromosomes using a camera lucida on my microscope. That was before the days of cameras perched atop the microscope. Anyway, armed with this new information, when I got back to Baltimore, my first bone marrow preparations in chromosomes worked beautifully, because I followed the directions that I had made. And my little lab didn't look back after that time, because we could make chromosome preparations and all sorts of things, and that's why I was able to make these chromosome preparations in the Turner patients that I just described earlier. So that was a big problem to actually get somebody to make - and I couldn't find anybody to make chromosomes. I had to struggle to make chromosomes myself. It worked, and so these are what I remember as some of the big problems in my life too.

[6]. SCOTLAND: GENETIC COUNSELLING, RELIGIOUS OBJECTIONS

You asked me about other things in, other advances in genetics, and I'd have to say, of course, chromosomes is only one part of it and for my purposes, I was also counselling children and parents and families with other genetic disorders, a wide range of genetic disorders at my clinic. We developed slowly, over two or three years, developed a service for all of the west of Scotland and this was a population of about five million. So we formed the West of Scotland Regional Genetic Service, so that was the basis of the genetics programme for that part of the world. This is one of the earliest regional service groups. And so while we were there of course the opportunities developed, and it was possible to make the diagnosis of chromosome abnormalities and other genetic disorders from 1967/68 onwards, from samples of the amniotic fluid in

pregnant women, so that we were able to make the diagnosis in some of these conditions, severe genetic conditions, in the foetus, and this gave parents who wanted this the opportunity of interrupting the pregnancy and trying at a later time to have another one. So my wife had joined me at that time and we were, or by then - several years before that actually - to work in cytogenetics, and she got involved in doing this prenatal, in developing this prenatal work with amniotic fluid cell cultures.

And we were able to collect a number of diagnoses, in fact 70, I think, as I recall, diagnoses of women who had wanted their pregnancies tested. And some of these women came from Ireland and some of these women were in Scotland. But the result was that in the majority of cases we were able to reassure these women that they were carrying a normal foetus. I think out of the 70 only one individual had, one pregnancy was affected with Down syndrome and that was the only, there was another genetic condition that was terminated as well, but there were only two pregnancies that had to be stopped. And so the general benefit was that women were encouraged to have pregnancies whereas they wouldn't have had these pregnancies had they known that there was no test. So we felt that there was a lot of criticism about what we were doing; my wife and I were accused of being Nazis by the Archbishop - the Roman Catholic Archbishop of Glasgow - and various other people were very much against what we were doing. It was particularly ironic because my wife spent part of her career in a concentration camp in Germany, and so she knew what the Nazis did and perhaps rather better than the Archbishop did. And she didn't like being told that she was behaving like a Nazi because she was providing a service for people who genuinely had a big problem and we could help them with. So one of the other difficulties I had, if you like, was to try and convince the Archbishop and various other people that what we were doing was needed and was the right thing - in fact was part of pastoral care which they should have been providing - but I never was able to persuade the Archbishop, I have to say, nor the Pope or anybody else in the Roman Catholic hierarchy. But that didn't stop us. I was convinced by the needs of parents and, you know, I didn't approve of abortion for social reasons, but I certainly was sympathetic to women who had these very big problems with having severely handicapped children. And that's what happened. And of course when prenatal came into the business, when we were able to give prenatal diagnoses, and my wife's paper on this subject was the first published in the United Kingdom, when we were able to provide this service, it increased the amount of genetic counselling that was done throughout the country, and suddenly there was something genetic counselling could achieve through testing pregnancies. So suddenly genetic counselling became very much more important than it had been, and genetic clinics were enlarged.

[7]. SCOTLAND: PRENATAL DIAGNOSIS

And also associated with prenatal diagnosis was ultrasound and in this town, in Glasgow, the pioneer of ultrasound was Professor Ian Donald, a friend and a colleague of ours, next door neighbour actually. And he was also very strongly against social termination of pregnancy, but his, the first patient that he terminated a pregnancy in the patient, was a pregnancy where there was a very severely abnormally affected child. So although he was against social terminations, he helped to convince other people that this was a correct part of obstetric practice. And the fact that we needed sonar ultrasound examination, we used it first of all to determine the age of the foetus to make sure there wasn't any twins, to locate where the placenta was so that we didn't hit the placenta when we were sticking a needle in. Ultrasound developed as a result of prenatal diagnosis so companies made better machines and so on, and that led to the better visualization of the foetus *in utero*.

So abnormalities could now be seen in the foetus, and I trace the start of all that to the work that we were doing with Ian Donald with amniocentesis in these very early days in 1969/1970/1971; these were the years that that was happening.

[8]. USA & UK: CHROMOSOMES & WORKING WITH MY WIFE, MARIE

Well, one of the most important things that happened to me when I spent my three years in the United States was to meet my future wife. And she was actually working as a student. She was doing some student work while she was going through college, and this was clerical work for Dr Victor McKusick, who was my

boss at Johns Hopkins. And every time I went into my office to look down my microscope at chromosomes I would have to pass her desk. And after saying good morning a number of times, I eventually, I had the temerity to invite her out, and so we got to know each other very well, and eventually we married, and our first child was born at Johns Hopkins. And my first child, I'm very proud to say, is a Professor of Genetics at Cambridge, so there must be something good about that experience. Anyway, Marie, my wife, was detailed off to help in some buccal smear surveys that I did when I just arrived in Baltimore. I mentioned previously that I'd been doing this in Scotland, and so as we did the same thing in the mental institution in near, in Maryland, near Baltimore, and it wasn't the least bit like a National Health Service institution, it was really a very depressing place. But that's another story.

But what we had to do was to go through the wards in this particular asylum, with permission, of course, to collect smears of inside the cheek in these handicapped children, and it was quite a - you know - sort of mass production thing, because we had to do very many, several hundred people, and Marie was there to mark the slides and write down the numbers and to make sure that we didn't get patients muddled up, we got the right sample from the right person. And during that exercise we discovered several new different types of chromosome abnormality and individuals with Klinefelter syndrome that had three X chromosomes as well as a Y chromosome, and we found individuals that had, female individuals that had three X chromosomes instead of two. And this was all apparent from the buccal smears. But anyway, Marie was involved in doing that, and when we went with our baby back to Scotland in 1961, Marie joined me in my lab. I had a grant from the United States to continue some research, and so Marie was employed on that grant. She was an American citizen and I was funded by the University of Glasgow, because I had a lectureship. So we were not funded by the same people. We had quite different bosses.

Anyway, so she joined in the work of chromosome analysis with me, which she had already done in, she'd already been involved in this in Baltimore, of course. And so we've been working together ever since, you know. That was 1960 to, well, 2015. No, she stopped work actually in 1993, but up 'till 1993 she was working in cytogenetics alongside me. We'd been working all that time together, and it worked out quite well. We didn't divorce and we had many, many, many arguments, of course, but we brought up four children, and we had a very happy career together.

[9]. FROM CHROMOSOMES TO EPIGENETICS & GENE-EDITING

Well, you asked me what I think for the future. You're taking this interview at a meeting discussing human gene mapping, and this is another area I haven't mentioned, which I have been closely involved since I left the United States, and I think I came to the conclusion at this meeting that human gene mapping was now a thing of the past, and the mapping that we do now is with mapping, looking for similar sequences in animal chromosomes and other vertebrates, and that's a different story. What is ahead of us in human genetics that's important? Well, you know, if we were to stick with looking at chromosomes, we still don't know an awful lot about chromosomes; in particular we don't know about the 200 different proteins that are involved in the structure of a chromosome. We know about a few of them. And I think there's a great deal to be learnt from looking at the proteins. And we've spent a lot of time looking at DNA, and DNA is very important, but we haven't spent enough time looking at the other proteins - not other proteins because DNA isn't a protein, I guess, it's a nucleic acid. Anyway, so I think a lot has to be learnt from looking at the proteins in chromosomes, that's one thing. It will help us to understand about how chromosomes pair during meiosis and how, and all the problems of combination. We know that chromosomes pair and recombine with, after double strand breaks, but only a tiny number of these double strand breaks produce crossovers, for example. And we don't know why that should be. So there are lots of questions about chromosomes that we need to learn, and we only can learn about them if we would spend a bit more time studying the chromosomes. That's one thing.

Another thing that interests me greatly is the area called "epigenetics". These are factors which influence the expression of genes in tissues, and one of the aspects of that, which is particularly interesting, is that there can be environmental effects which have transgenerational effects, you know, from one generation to the next, which we don't totally understand. We know about things that modify DNA, but we don't totally

understand what, all about epigenetics, okay? And the third thing that we could learn a little more about is how genes are regulated. We know a little bit about how genes are regulated but there are a lot more DNA sequences which are involved in gene regulation, than there are actually genes that make proteins. So we should learn a bit more about that. Then I have a particular interest in non-coding DNA because I believe that the rest of the, much of the rest of DNA, which has been regarded as "junk" up 'till now, I never believed in "junk", and I would plead with people not to talk about "DNA junk". They should study it a bit more and find out what it does, it's not junk. Anyway, I believe that non-coding DNA is worthy of a lot more study, because it will tell us a bit more about the natural history of chromosomes and how chromosomes behave.

Then finally, perhaps a little touch on something that's very, very topical and that's the possibility of editing genes. In other words, looking at gene, type of gene therapy in which you can actually correct abnormalities, mutations, in genetic material in living people. At the present moment this has been started just recently, and the trouble is at the moment we edit lots of things that we don't want to edit, and we have to be a bit more specific about what we're editing to get it right. But I mean clearly the method is very promising, and there will be a way of doing this properly in the future. So I think that's something that people can quite, with advantage, go into and study in the future, because I think it has a lot of potential.

[END OF TRANSCRIPT]

Further related resources:

1. Christie D A, Tansey E M (eds) (2003) *Genetic Testing*. Wellcome Witnesses to Twentieth Century Medicine, vol. 17. London: Wellcome Trust Centre for the History of Medicine at UCL.
2. Jones E M, Tansey E M (eds) (2014) *Clinical Molecular Genetics in the UK c.1975-c.2000*. Wellcome Witnesses to Contemporary Medicine, vol. 48. London: Queen Mary, University of London.
3. Jones E M, Tansey E M (eds) (2015) *Human Gene Mapping Workshops c.1973-c.1991*. Wellcome Witnesses to Contemporary Medicine, vol. 54. London: Queen Mary University of London.