Ferguson-Smith, Malcolm

Personal Details

Name	Malcolm Ferguson-Smith
Dates	Born 1931
Place of Birth	UK
Main work places	Glasgow; Cambridge
Principal field of work	Human Cytogenetics
Short biography	See below

Interview

Recorded interview made	Yes
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Personal Scientific Records

Significant Record set exists	Yes
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Biography

Malcolm Ferguson-Smith is currently Research Professor in the Department of Veterinary Medicine, University of Cambridge, UK. He was born in Glasgow in 1931, and graduated in medicine at Glasgow University in 1955. He was a Fellow in Medicine at Johns Hopkins in 1959 and he remained there working on chromosomes for nearly 3 years. During this time he established the first chromosome diagnostic service in the USA and undertook cytogenetic research into the Turner syndrome. Returning to Glasgow University in late 1961, he was appointed successively, Lecturer, Senior Lecturer and Reader before becoming Burton Professor of Medical Genetics in 1973. In 1987 he was appointed Professor and Head of Pathology at Cambridge University and Director of the East Anglia Regional Genetics Service. On retiring from the headship of Pathology in 1998, Professor Ferguson-Smith and his research team moved to the Department of Veterinary Medicine, to establish the Cambridge Resource Centre for Comparative Genomics. He was elected Fellow of the Royal Society of Edinburgh in 1978 and the Royal Society of London in 1983. In 1980 he became the founding editor of Prenatal Diagnosis. With J.M. Connor his undergraduate textbook "Essential Medical Genetics" has run to five editions.

INTERVIEW WITH PROFESSOR MALCOLM FERGUSON-SMITH, 5th DECEMBER, 2003

This is 5 December 2003 and I'm talking to Malcolm Ferguson-Smith in his office at the Veterinary School in Cambridge.

PSH. May I ask how you got interested in genetics in the first place?

MFS. At Stowe I did a Higher School Certificate in Zoology and Botany among other things and I remember being fascinated by chromosomes. I left school in 1949 and then I forgot all about them.

PSH. It must have been a very enlightened place to show you chromosomes in school at that stage.

MFS. Well we learned about Mendel and genetics. We looked at chromosomes of plants, and at meiosis. I was very interested in trees, in fact I planted lots of trees at school and that was one of my hobbies. And then I went to University and won a bursary in botany, because I still had maintained this interest (although I was doing medicine). After graduating in '55 in Glasgow, I did my house jobs there and then my idea was that in order to train to be a physician, I thought that it would be good to go into pathology because I thought if one understood the science of disease then one would be better placed as a physician. And my father had done the same thing too, so I was influenced by him.

PSH. He was a dermatologist, is that right?

MFS. He was physician for diseases of the skin at Glasgow Royal Infirmary. He had wards there for over 30 years. And so I applied for an SHO job in pathology and Professor Cappell said "Why do you want to do pathology?" and I said "I am not interested in a career in pathology. I really want to train to be a physician and I feel the best way of doing so is to learn something about pathology". He replied "there is much competition for places and we only take people who really are going for a career in the subject . . ". To cut a long story short, the next day I got a letter offering me the job. So during that time (in 1956) doing my PMs and surgicals, I came under the wing of Dr Bernard Lennox who was at one time a Pathologist at the Hammersmith. He had just come to Glasgow about a year or so before I arrived on the scene. Now, he was the Pathologist who worked with Paul Polani in discovering the absence of sex chromatin bodies in Turner's syndrome. This is the Polani, Hunter and Lennox paper in Nature in 1954.

In 1956, Bradbury, Bunge and Boccabella in the United States had identified individuals with Klinefelter's syndrome that had sex chromatin positive nuclei and were believed to be sex-reversed females. Bernard Lennox suggested that I join him in some research to see if we could find some Klinefelter

cases.. He was responsible for suggesting to me that we use the buccal smear technology. So I got into genetics by doing buccal smears.

So Bernard said "First of all I think you should go along to the urology clinic and screen patients with undescended testes". The Chief of Urology happened to be a personal friend of the family, a Mr Willy Mack, and so I did lots of buccal smears on children who were just about to have their testes descended. None of them turned out to be chromatin positive. I knew that Mr Mack ran an infertility clinic. So I said to him "These patients with Klinefelter's syndrome are all infertile so why don't we look at some of the infertility

clinic patients?". And Mr Mack said OK, and to cut a long story short in a few weeks time I had moved my screening to the infertility clinic. The 8th person I looked at was a patient with Klinefelter's. This was very exciting, so I looked at a few more and, to cut a long story short, 11% out of quite a large number of patients with azoospermia and oligozoospermia were found to be Klinefelter's [see Lancet, 1957 ii:167-169]. That prompted me to look at the testicular histopathology of infertile males and, as Mr Mack was in the habit of doing testicular biopsies on azoospermics, I went back to the pathology records and took out all the slides of these patients and sure enough I found lots more Klinefelters. I became expert in looking at the histopathology of testes and, of course, Mr Mack biopsied these new patients with Klinefelter's syndrome.

Now after while a young man who was being medically examined for the Army was found to have small testes. He was referred to Mr Mack to determine the cause of his hypogonadism. He had a testicular biopsy which I examined and in that testicular biopsy I found a tubule full of spermatogenesis [see Scot med J 1958, 3:39-42]. I was very excited to find a sperm and lots of spermatocytes. In the spermatocytes, I could see sex vesicles. I knew what the sex vesicle was, it was the condensed X-Y bivalent. So I went along to Bernard Lennox and I said, these guys are not sex-reversed females, because this patient has a Y chromosome. We talked about this and decided that we needed to find someone to look at his chromosomes. So I went along to see Professor Pontecorvo and I don't think he was terribly interested. He said "well nobody looks at chromosomes nowadays ….we are all interested in biochemical genetics. However, you should talk to our cytologist, Charles Elliot, who is looking at the chromosomes of Aspergillus." I went to see Charles and explained that we'd got a lot of these patients that everybody thought were sex-reversed females, but I had found a Y chromosome in the testis. I thought that they needed to have their chromosomes looked at. He replied "I don't look at mammalian chromosomes but I know a chap called Charles Ford who is working in this area". This was about a year after Charles Ford and Hamerton had confirmed in Nature (1956) the chromosome number of 46 in human meiosis. And he wrote to Charles and I eventually spoke to him and told him that we are doing these testicular biopsies. He said "if you find this again in the testes then you can make meiotic preparations and see what is going on". So that was very helpful. He also told me that he was working on a bone marrow method to look at human chromosomes. "It's nearly ready but when it is ready, I will write to you and you can send me some material from these cases". He knew nothing about Klinefelter's before

I told him. Then, to cut a long a story short, this very disappointed young man picked up Nature one day in 1958 and saw that Charles Ford had not only presented his method for doing bone-marrow preparations but had included in the last paragraph a patient with Klinefelter's syndrome which he had got from Robertson Smith in London. He found that this patient with Klinefelter's syndrome had 46 XX chromosomes. So Charles presumed that Klinefelters were sex-reversed females. I always thought that it serves him right! If he had looked at our cases he would have discovered that they were XXY. But he looked at another case which happened to be a rare XX male. He thought later on that this must be an XX/XXY mosaic because he had only looked at bone marrow, but this was never proved. I think he had the first XX male. Anyway, I was a little disappointed by this. Meanwhile, before Charles'publication, I had been going into the urological theatre with Mr Mack and every time a Klinefelter patient had his testicular biopsy I took a little bit of bone marrow from his sternum. (I have to say I did ask the patient beforehand but there was no written permission).

PSH. No ethics.

MFS. So these poor patients woke up with a little hole in their sternum. And I trotted off with this marrow sample, and part of the testis biopsy for meiotic preparations, and I tried to do what Charles Ford had told me. I have some pictures of these awful preparations I made and they are absolutely impossible, mostly because of dust around the place. You really can't count the numbers of chromosomes except with hindsight. I was frustrated with this so I went along to my Professor and said look nobody here is interested in doing the chromosome analysis and he told me he had heard from Douglas Black of somebody in the United States called Victor McKusick who was setting up a medical genetics group. To cut a long story short, Douglas Black saw Victor McKusick and Victor McKusick contacted me and invited me to come to Hopkins on a Medical Fellowship to try and get this bone marrow business right.

PSH. Can I just go back a tiny bit from there. This must be now about 1957, 1958.

MFS. That's right. The summer of 1958

PSH. So the discovery of the human chromosome number, 1956 and then Paul Polani was working with Charles Ford on Turners and then am I right, Pat Jacobs had done something then in '59 on Klinefelter's, so we haven't got to there?

MFS. No not yet. Pat got it right about XXY in '59. She went to Oxford in 1958 for some months to have some training with Charles Ford and Lazlo Lajtha (the haematologist) to learn marrow culture for radiation studies with Court Brown. Then went up to Edinburgh. . Yes, I have missed out quite a lot of the story, trying to shorten it a bit, but of course in Glasgow I was continuing with the buccal smear screening. Some of our Klinefelter patients in the infertility clinic were a bit dim, and some had been to special schools. So I thought that perhaps this condition is associated with mental handicap". So I went out to Lennox Castle. This was at the end of '56,'57 and screened all

the males and 1% of them had Klinefelter's syndrome [Lancet 1958, i:928-931].

PSH. This was a mental subnormality hospital?

MFS. That's right. And it was a very nice one. They were all well looked after, everything was really good compared to those I experienced later in the United States. At that time there were a lot of meetings about nuclear sex, so our data on infertility clinics and preliminary observations on mental deficiency were presented at a symposium on nuclear sex in London in 1957 organised by Robertson Smith. I met Murray Barr there. He was very kind to me. He encouraged me to get on with this work. In fact his discovery of sex chromatin really put Polani and me on to trying to solve the paradox of abnormal nuclear sex in Turners and Klinefelters respectively.

PSH. He was at London, Ontario?

MFS. He was at London Ontario and I went to visit him a few years later. We kept in touch over that time.

PSH. Am I right that your initial chromosome work was a mixture of bone marrow and meiotic preparations?

MFS. Yes. I took a little bit of testis material from biopsies and tried to make meiotic preparations, but there were never any meioses in it. This is very very rare to see.

PSH. So the testicular material was for nuclear sexing and the chromosomes were . .

MFS. Well it was mainly to look at the testicular histopathology. I worked out that the histopathology was rather special in Klinefelter's syndrome. One of the things that I found was that the tubules in patients with Klinefelter's syndrome were not lined with elastic fibres. In all cases of post-pubertal atrophy, the hyalinised tubules had elastic fibres around them. The exception was Klinefelter's syndrome and, this meant that the pathogenesis occurred before puberty

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PSH. You got to Baltimore in which year Malcolm,?

MFS. McKusick invited me to start in October '58. As I wanted to complete some work, I postponed my departure until January 1959. As I went across in the Carinthia from Liverpool to the United States via Halifax, Lejeune's paper on Down's syndrome came out. I learned about it as soon as I stepped off the boat in early February 1959., but anyway, I got to McKusick's and of course there was no equipment. Absolutely no lab and no microscopes. I eventually got a cupboard in Moore Clinic. A tiny little room off the secretary's office.

PSH. I think I remember which it was – yes.

MFS. It was much smaller than this room. Eventually, I managed to persuade them to get me a microscope and, in the next few weeks, I'd got the bone marrow method working and we looked at Down's syndrome of course. One of the first things we did was to go out to the State Mental Institution at Rosewood to take bone marrow samples from Down syndrome patients. Do you remember it?

PSH. I remember it indeed.

MFS. I remember we started a buccal smear survey there early in the year and picked up the first XXXY cases for another paper in the Lancet. At McKusick's we gathered a few students together to help in the research. I met Marie in Moore Clinic.

PSH. Yes let me stop there. That was a pretty important aspect. What was Marie doing at the time?

MFS. Marie was a student doing part-time work, earning a little money in order to help her go through college. She did reference filing. She was asked to go to the library and get references and write out reference cards both for McKusick and Abe Lilienfeld, who was the Professor of Public Health. Remember Abe?

PSH. I do, in epidemiology

MFS. I had to pass her desk every morning to go to my cupboard and one day I asked her out. We used to go sight seeing and sailing etc.

PSH. These are parts of history which either never get into the papers or people tend not to sort of take them into account in working out how things happen and yet they are terribly important on a personal basis.

MFS. Stan Handmaker, who was a student at Hopkins at the time, also joined our group. He and I would go out to Rosewood to do these buccal smears. Stan was a very nice chap, but he used to get his figures all muddled up. He wasn't very good at record keeping. So I decided to take Marie out to help with the paperwork, to write down the names and put the numbers on the slides, so that we didn't make any mistakes. From then on we didn't make any mistakes. I had another student called Dick Hill who volunteered to have a sternal puncture so that we could get some normal chromosome material. That was in 1959, before the blood sample method was introduced. As I mentioned, we studied several Down's syndrome using bone marrow at that time. Then I thought it would be a very good idea to go and visit Albert Levan at Easter of 1959. Everything happened so very quickly.

PSH. Yes

MFS. Albert Levan used to visit T C Hsu in Houston for a few months each year so I thought I had better go and visit them. So I got myself invited to talk about Down's syndrome. I showed Albert Levan my preparations and he showed me how to use the camera lucida to make drawings of chromosomes. Albert Levan was very important in this field; he had developed colchicine as a

mitotic poison in onion root tips to accumulate mitoses. He was working on mice and rats at the time, and showed me how to make these wonderful camera lucida drawings. I persuaded him to come up to Hopkins a few months later in the summer of 1959. He came and brought his camera lucida equipment, and we sat down in my cupboard and we drew pictures of Down's syndrome chromosomes and he and I figured out that the one that was extra was the smallest whereas Lejeune had called this chromosome "21". Albert and I agreed that this was a mistake. The chromosome trisomic in Down syndrome was chromosome 22. I got into fearful trouble ever afterwards trying to convince everybody that it was chromosome 22 and not 21, as of course it is. Even up to 1970 I tried to get the nomenclature changed but everybody said . . .
PSH. Too late.

MFS. Anyway I learned how to make camera lucida drawings. However, I happened to have a single lens reflex camera, so I got an attachment to put my camera on top of the microscope and from then on I gave up the camera lucida drawings and took my own photographs. That was again in 1959.

PSH. Am I right that Tjio also was a very great photographer in terms of using actual photomicrographs rather than drawings.

MFS. Correct. But of course cytogeneticists were using photomicrographs before that. TC Hsu was as well. But I think they only photographed their very best preparations and they didn't do it routinely. But I took chromosome photographs of all the cases we looked at.

PSH. When did you come back to Glasgow from Baltimore?

MFS. I had a year's fellowship in medicine and the deal was that I should come back when it finished, but I was really switched on by Medical Genetics by this time and I decided that what I wanted to do was to try and help introduce genetics into medicine. I felt that medicine had really not paid much attention to genetics and that chromosomes would be one way in. Professor Cappell had said he would fix up a lectureship for me. This took some time because Pontecorvo and Cappell were arguing about whether this lectureship should be held in Pathology or Genetics, and this took a bit longer. So McKusick offered me an instructorship. So I took that up for the next 2 years.

PSH. Did you have 3 years in Baltimore?

MFS. Yes, I went back in November 1961, and took up my lectureship in the Department of Genetics because Pontecorvo had won the argument with Cappell. I had an honorary associate position in the Department of Pathology.

PSH. Was Genetics in its new building at that time?

MFS. No it wasn't. I found myself in the old Anderson Department of Medicine, the original little school of medicine at the corner of Church Street and Dumbarton Road, in fact in beside the dermatologists. This was the old Andersonian Institute where David Livingstone among others had been a student. I had a room at the back and we set this up as a small lab. I was still

in contact with Bernard Lennox and he had found a person to work with me called Patricia Ellis and so she joined me and Marie, who started doing all the photography. I had an NIH grant at that time which paid Marie's salary and provided research expenses.

PSH. So when did you start broadening your cytogenetics to what you might call medical cytogenetics as a service.

MFS. At Hopkins. My lab became the first chromosome diagnostic lab in the United States. I got material from all over the place, and in 1960 particularly, we were very active because we were beginning to use blood samples by that time. And one of the most important people for me at Hopkins, apart from Victor, was Lawson Wilkins who was a pioneer in paediatric endocrinology. He had a tremendous clinic, which I attended every Saturday morning, for children with ambiguous genitalia. We saw a great variety of sex disorders particularly salt-losing adrenal hyperplasia, Turner's syndrome, short stature etc.. He was a most meticulous clinical scientist. He kept fantastic records, wonderful graphs of development of height and weight and lower-segment-upper segment measurements, hormone and steroid levels etc. He was intrigued by the sex chromatin and sex chromosome results and he let me study all his patients with Turner's syndrome and with male pseudo-hermaphroditism. The clinical material was absolutely wonderful and this formed the basis for my major project on Turner syndrome. This was perhaps the most important study I ever did. The other influential person in my work at the time was Howard Jones.

PSH. Yes.

MFS. He was Professor in obstetrics and gynaecology and had a particular interest in true hermaphroditism. Our first cases of true hermaphroditism were reported in Lancet [1960 ii:126-128]. Anyway, so what did we do with those Turner cases? Well I was intrigued why these 45.X Turner patients had shortened stature and all these malformations. At the same time Mary Lyon was writing that there was nothing wrong with XO mice, and that this meant that one X was sufficient. The other X chromosome wasn't really important. I argued that this doesn't work in humans because two Xs, or an X and a Y, must be important, otherwise human XOs wouldn't have all these malformations. At that time I reviewed all the literature and assembled all the patients that everybody else had looked at, noting their clinical features. I classified them according to mosaicism, or whether they had structural abnormalities of the X or Y. Over the next two years I came up with the theory that the reason why humans with XO were abnormal was that they lacked the full dose of certain genes which escaped X-inactivation and which had active copies on the Y. The equivalent genes were not present on the sex chromosomes in mice.

PSH. Right.

MFS. Moreover, in individuals who had deletions only of the long arm of the X chromosome their stature was within the normal range and lacked all the other features of Turner's syndrome therefore those genes that were important must be on the short arm of the X chromosome. Individuals with

deletions only of the short arm of the X had the full Turner syndrome. This study ended up in an early paper in the Journal of Medical Genetics.

PSH. When was that because I was looking through your early papers for that and for the mechanism of X-Y pairing?

MFS. Well that paper was eventually published in '65 [vol 2,142-1550]. I tell you why it was 'eventually' because I had the greatest difficulty in getting it published. Nobody would accept it. It was thought that Turner's syndrome was caused by the loss of cells in the early embryo because of random inactivation of the single X and consequent cell death. Everybody accepted Mary Lyon's view that in mammals you only need one X chromosome. My haploinsufficiency hypothesis was regarded as heretical. I eventually persuaded somebody in the Journal of Medical Genetics to publish it as a review. All the cases we studied at Hopkins were published a bit earlier in Cytogenetics, but my review of the literature was in the Journal of Medical Genetics. It became a Citation Classic in 1991.

When I came back to Glasgow and set up my group in Anderson College I continued to look at Klinefelter's. I picked up all the Klinefelter's that I had studied before, and got their blood samples and looked at their chromosomes. I had over 130 patients with Klinefelter's syndrome. So after doing Turner's in the United States we worked on the Klinefelter's in Glasgow., Not only was I taking blood samples but I was talking to all these patients on family visits, with my Isihara colour vision plates to determine the parental origin of non-disjunction. We looked at their Xg groups, at least Rob Race and Ruth Sanger did for the same purpose, I found, that all those patients in which the extra X chromosome had come from the mother had a significant maternal age effect and all those cases that came from the father didn't. So that was, I thought a nice correlation showing that a maternal age effect was important in maternal non-disjunction of the sex chromosomes. It was based mostly on Xg types. In the course of this, several of my Klinefelter patients turned out to have no Y chromosome. I can remember the first one very well. He was a naval officer. There seemed to be something different about these XX males, They were not tall, in fact, they came into the female stature range, they didn't have learning deficits, and they didn't go to special schools. And so when we got the answer back from Ruth Sanger that some of these males had failed to inherit their Xg allele from their father this was of great interest. Of course, the explanation then was that these must be undetected XXY mosaics. Then I had this eureka moment. . . I can remember that it happened on a train to Birmingham. I suddenly realised that they must have swapped the Xg locus on the X for the sex determining locus on the Y as a result of accidental recombination outside the pairing region.¨ I then wrote it up within about a week and submitted it as a short article to the Lancet where it appeared under "hypothesis". That was in 1966, and the implication was that the sex determining locus
was on the differential side close to the boundary of the pairing and the non pairing segments of the Y chromosome and also that the Xg locus had to be on the differential side of the boundary on the X. All this was confirmed 20 years later when molecular methods became available and SRY, the testis determining factor, was discovered at the predicted location.

PSH. You obviously must have had a lot of contact with Race and Sanger at that time.

MFS. Yes. They were wonderful colleagues.

PSH. And did you link much with Paul Polani, because he was doing rather comparable things with Turner's in terms of colour vision, and then later Xg.

MFS. The colour vision studies happened even before the chromosome abnormalities were discovered. When we were doing the buccal smear surveys I contributed my data on colour vision in Klinefelter patients to the Nature paper in 1958 by, Polani, Bishop, Lennox and Ferguson-Smith et al. The Xg blood group became available in1962. So some of the data was based entirely on colour vision and in Turner's syndrome the frequency of colour vision defects was the same as in males and in Klinefelter's syndrome it was nearer females and that was taken as evidence that they were sex-reversed. So all that went on even before the Xg and chromosome studies and so I was aware of its value early on. However, nobody had twigged the implication of the Xg findings in the XX males,

PSH. It has always interested me that these really first fundamental steps in cytogenetics were virtually all European and yet the original studies of chromosomes in insects and things were mostly American.

MFS. That's right, Calvin Bridges and Thomas Morgan at the fly lab in Columbia were pioneers of the chromosome theory of heredity and T.S.Painter nearly got the chromosome number in man in 1923.

PSH. There must have been very good links between the different European and I suppose also international groupings generally, and everything then did happen very rapidly didn't it in that year or two.

MFS. Boveri of course was an exception and that wonderful institute in Naples that gathered all these zoologists together working on early chromosomes of sea urchins. That was at the turn of the century, and of course some of the best cytogeneticists were in Russia. There were a few in the United States, but I think in Europe there were still lots of cytogeneticists in those days. In 1959, with a few exceptions, almost all the results came from the UK; the exceptions were trisomies 13 and 21. Very soon, with the introduction of short term blood cultures, medical cytogenetics became an international venture.

There were other things that I was involved in during those early days of human cytogenetics. I really got interested in chromosome identification and in meiosis. One of the things that we discovered in the '60s was that Lejeune was wrong in the identification of chromosomes 13-15 and 21-22. He believed that they could be identified from the presence or absence of satellites. We had done an enormous amount of work analysing lots of photographs of metaphases and cutting out karyotypes from many cases. I was able to show a photograph in a Lancet paper in 1960 in which all these chromosomes had satellites at the ends of their short arms. Every single one of these 5 pairs of human acrocentric chromosomes were satellited. Then there was also a

paper in 1957 by Yerganian 1957 who had looked at the nucleolus organiser regions in human meiosis. He thought that the nucleolus locus was right in the centre of a pachytene bivalent rather than at the ends of acrocentric chromosomes that we had observed.. So with the help of Mr Mack producing the testicular biopsies for me, I looked at pachytene chromosomes and realised that what Yerganian had been seeing was two acrocentric chromosomes sticking together by their short arms and forming a common nucleolus. I had made squash preparations without using hypotonic so that the nucleoli were retained at pachytene attached to the ends of the chromosomes. In some cells up to five pachytene bivalents could be seen joined together in a common nucleolus. This was what I had described as satellite association in somatic metaphases in another 1960 Lancet paper. The tendency of these chromosomes to stick together was probably due to either the fusion of nucleoli or the pairing of homologous regions at the ends of the acrocentric chromosomes. This explained the origin of Robertsonian translocations, the commonest type of structural abnormality. During meiosis there was an abnormal recombination between these repetitive areas, producing metacentric chromosomes. You could distinguish chromosome 21 from 22 because 21 was shorter and because the patterns of chromomeres on these chromosomes were so distinctive.

PSH. And you were really doing most of this yourself.

MFS. Yes.

PSH. Just to move away from that for a bit, but I want to come back to it. When you were at Glasgow there were some other interesting folk there, one of them was Jim Renwick, and am I right you took on his linkage lab after he left?

MFS. Yes. The reason I started working with Jim was that we had observed a number of striking chromosome polymorphisms that could be used as chromosomal markers in linkage studies for chromosome mapping. I got a grant from SHERT to do this, with Jim Renwick's lab and Marion Izatt doing the blood groups and Pat Ellis and Marion Stone in my lab doing the chromosomes. We had too few blood groups for this to be a success but were able to determine some regions in which loci could be excluded from parts of the map. Earlier we had become aware of differences in the pattern of individual chromosomes, so were able to measure the size and the centromere position of specific chromosomes. In this way we were able to work out a standard karyotype, and some of the features on the standard karyotype that we published, in 1962 called secondary constrictions, were useful identifiers. In fact these secondary constrictions were G band negative areas which were the precursors of the banding patterns observed by others 8 years later. For example there was a very important one on the short arm of chromosome 6, right in the middle of the short arm. This was a pale area which enabled you to identify chromosome 6 very nicely and there were similar patterns on other chromosomes including chromosome 9 and chromosome 11. Eventually the way that we worked it out, the way that we set out our karyotype was exactly the same as it turned out from banding after 1970.

PSH. This would have been sort of ’68, ’69 time would it?

MFS. Yes, The SHERT grant was awarded in 1968, the year Jim left Glasgow for UCL.

PSH. The other area I want to touch on a bit in your Glasgow time, was the development of prenatal diagnosis because you were really at the absolute beginning of that weren’t you?

MFS. The reason we got into that was through our study on abortions. I don’t know if you remember David Carr and André Boue.

PSH. Yes I do

MFS. They were getting very interested in looking at chromosomes in spontaneous abortion material, particularly David Carr. So we started this in about 1968 when I had one lab in the Genetics Department in the University, another lab out at the Queen Mother’s Maternity Hospital which was the source of our material. Moyra Smith was doing her MD with us on this work. Then the paper by Roy Breg and Steel came out in the Lancet in 1969 saying that they had managed to get amniotic cell cultures. Marie was actually growing amniotic cells from fetal membranes at the time, so it was a very easy step for us to obtain amniotic fluid from hysterotomy specimens, and that was in ’69. I am ashamed to say I had given a talk in 1963 in London. It was at a meeting of the old Galton…... . .

PSH. Old Eugenics Society.

MFS. Old Eugenics Society. I announced that I thought it unlikely to get cultures from embryos early enough to give the mother the opportunity of terminating the pregnancy. One of these unfortunate wrong predictions! And of course Marie and I were busy several years later showing that we could, and so there wasn’t anything particularly original about what we did. We just followed what they had done in the States, but we were one of the first UK groups to publish on Down syndrome prenatal diagnosis (in 1971 in the BMJ) because we happened to be working with abortuses at the time and it was an easy thing to get amniotic fluid.

PSH. When did you start the journal Prenatal Diagnosis?

MFS. That was in about 1979. John Jarvis from Wiley’s came along to see me after they had put out a circular saying “does anybody think it a good idea to have a journal on prenatal diagnosis?” and I was one of the few people who thought we had far too many journals. I didn’t see any reason why we should have another one. Jarvis saw this as a good reason to persuade me to be Editor. I said I don’t want to do it. I want to have a journal on gene mapping instead, and this was before Genomics. Wasn’t it? When did Genomics start?

PSH. Genomics was later I’m sure.

MFS. [Genomics started in 1987!] But everyone was excited about prenatal diagnosis. It would have been better if I had stuck to my guns. We were doing a lot of gene mapping then of course. That was another area I was very interested in.

PSH. What year was it that you moved from Glasgow to Cambridge?

MFS. '87

PSH. So by then you had built up, I know, a really big, comprehensive department in Glasgow. It must have been quite a wrench.

MFS. It was a terrible wrench. As you know, Victor McKusick had opened our new building in 1981. From 1975 onwards I had been trying to get more facilities for our lab, especially for prenatal diagnosis. So I went along to the National Fund for Research into Crippling Diseases, Action Research, and had a chat with Duncan Guthrie. I asked if there was any chance of getting a grant to build a few portacabins. He laughed and "What you want is a proper Institute. I'll guarantee a third of the money costs if you can get a third from the Health Service and a third from the University". The University didn't think we would get anything from the Health Service so agreed to a third, and the NHS didn't think we would get anything from the University so also agreed to a third.

PSH. So you got more than you needed.

MFS. It seemed that I had all the contributions that we needed. As the NHS had to build it I went back to them but they refused to go ahead "because the costs have gone up ". I threatened to have a conversation with the Daily Record and the Glasgow Herald so the Secretary of the Board said well then it will have to be a much smaller building. I then approached Hugh Fraser, you know of Harrods fame, and his mother. His mother, who chaired the Fraser of Allander Trust, agreed that the Trust would make up the balance and we got our institute. You may remember receiving the plans of the institute.

PSH. Yes indeed. So that opened in 19 . . .

MFS. It was 1980 yes

PSH. So uprooting from that must have been . . .

MFS. Yes it was difficult. We had 40 scientists in the department and a number of University staff, 3 consultants, the first registrar and the first senior registrar in the country, and we were flourishing. And so I remember one evening at home in 1986 the telephone rang "this is Richard Adrian from Cambridge, we have just appointed you Professor of Pathology" and I roared with laughter. I said "This must be a mistake. I haven't applied for any job in Cambridge. I didn't even know there was one". I pulled myself together when he identified himself as Vice Chancellor of the University and responded politely to the effect that I would certainly be glad to consider it. So Marie and I went down to see Richard Adrian and Marie said "What on earth do you want to appoint my husband for?" Richard Adrian was quite taken aback by

this! Anyway by this time I had realised that the Department of Pathology wasn't just a place that did post mortems and routine surgicals It was a huge research department of over 400 people, not 40 scientists, and was one of the top pathology departments in the country. Adrian explained that the electors wanted me to set up a genetics service as well as be Head of Pathology. They had been impressed by our service in Scotland. I explained that I would have to be able to continue my research and that I needed a flow cytometer for sorting chromosomes. (I thought they will never give it to me as it costs about £200,000). I also indicated that I would need two lectureships, one for John Yates and one for Nabeel Affara. I was astonished when I got a letter back accepting everything that I had asked for.

PSH. Amazing. One thing, just to jump on a year or two, how did you get involved with the BSE saga?

MFS. Right. That was towards the end of my time at Cambridge, at the end of '97 The Chief Cabinet Secretary, Sir Richard Wilson rang up and said we want you to consider joining a committee to look into BSE and I, of course said, like Marie
"Why me?" And it turned out it was because I didn't know anything about these disorders, hadn't been involved in the research and could be impartial. Eventually I heard a number of people had suggested me including the Chief Medical Officer at the time. Anyway that's when I heard about it, and then I met Nicholas Phillips and he came to Cambridge to talk to me. And we got on very well together. I have tremendous respect for him. You didn't need to tell him twice about something. He had a very retentive memory and anything in science that I wanted to talk to him about he would take in immediately. He would question all the ideas I had out on the science side of it, for which I had responsibility on the Committee. We were critical of the Ministry of Agriculture, Fisheries and Food, and I still remain very critical. It was a fascinating story, 16 volumes later. Unlike the researchers, I was able to overview all the science and was not focusing on any one particular part. This gave me a broad view of the mistakes that were made and how the epidemiologists thought about things. It was obvious, with the benefit of hindsight of course, how everybody was fooled into believing it was just simply scrapie getting into cattle, and as scrapie hadn't harmed anybody for 250 years BSE wasn't going to harm us now. And there was lots of evidence from very early on that this disease behaved quite differently from scrapie, particularly when the cats became affected. Cats were known not to be susceptible to scrapie, but nobody reviewed the science at this point. Nobody considered "what do we have to do now?". Nobody explained to the public how many people had taken infected food. It really was a tragedy and still is.

PSH. They were probably right to get somebody who wasn't from directly inside the field who could look at it in a dispassionate way.

MFS. There was no question of my being dispassionate, I became deeply concerned.

PSH. But you weren't constrained by previous ways of thinking.

MFS. No not at all. I reviewed 120 of these MAFF research projects, only 12 of them were peer reviewed and in most of them the principal investigator hadn't even bothered to write a final report. The amount of waste and the kind of stupid things they were doing and things they were not doing was unbelievable. This is not the way to do Government science.

PSH. No.

MFS. What MAFF should have done and what DEFRA is doing now a bit more, is to contract out their research work to the Research Councils. Unfortunately they are still retaining a lot of it because they have their hands on the bovine material.

PSH. Malcolm the very last thing I want to come back to is your comparative cytogenetics, because I think I am right, this was one of the very first papers you ever published, was on primates, wasn't it.

MFS. Yes we wrote a brief paper in Science in 1960 on the chromosome number of the chimpanzee. This was the first confirmation that the chimps had 48 chromosomes.

PSH. What was it that made you come back to this. Am I right that when you retired from the Pathology chair then this was the area you, with perhaps an interlude for BSE, but you came back to establish a lab with that as its main focus?

MFS. I have always tried to keep up to date with technology. For example, we were very early into in-situ hybridisation. First with Sue Malcolm as a post doc on a MRC grant in 1975 with the help of Bob Williamson, and we got cracking on using in-situ to map the exact chromosomal location of the alpha and beta globin genes and the kappa light chain gene. The new recombinant DNA technology allowed one to make lots of copies of probe. That was the secret. Our previous successes with gene mapping involved deletion mapping,, For example we identified the loci for red cell acid phosphatase on chromosome 2p and for the adenylate kinase locus on chromosome 9q using patients that had parts of their chromosomes missing, and who happened to have abnormal inheritance of the various polymorphisms. This was in the days when you didn't have DNA markers. You had only the 23 blood and serum polymorphisms and, of course, I had the legacy of the marker lab left by Jim Renwick,

In the 1970s we were also busy with prenatal diagnosis and screening, especially amniotic and serum AFP for spina bifida. This led into the serum screening programme and the UK Collaborative Study. Glasgow contributed the highest number of NTD cases to the Study. We kept all the serum samples from the Study and we were able to test for low serum AFP levels in Down's syndrome, and so the Glasgow Down's syndrome screening programme evolved from this work.

But to return to the comparative genomics studies and chromosome sorting, this all started with a phone call from Brian Young around about 1980. Do you know Brian Young?.

PSH. I know him yes.

MS . Well in those days he was working out at the Beatson Institute of Cancer Research in Glasgow under John Paul. He had been using a single laser flow cytometer to sort chromosomes from an MRC cell line and had difficulty interpreting the flow histogram and in identifying the chromosome peaks. I suggested that we should look at the results of sorting chromosomes from normal controls and see if this could be done from blood samples. So we made these fixed chromosome suspensions according to his method from a number of individuals that had been karyotyped., We correlated the flow histograms with the karyotypes and realised that there was a direct relationship between the size of the chromosome and the position of each peak. Shifts in the peaks could be correlated with chromosome heteromorphisms. An individuals sex could be determined from the area under the peak produced by the X chromosomes. It was really very exciting. Do you remember Peter Harris?

PSH. I do indeed.

MFS. Peter Harris did his PhD with me on developing the flow cytometer to follow chromosome polymorphisms and aberrations in families. I managed to get a grant from Action Research for a flow cytometer. This was in about 1981 and we were doing projects on measuring the size of chromosomes such as the size of the X chromosome in XX males and in Duchenne patients. For example, we found an old chap with Becker muscular dystrophy and this huge deletion of the X chromosome. He was a very bright chap but he had over a megabase missing from the short arm of his X chromosome. Quite extraordinary. We were also able to show deletions in individuals who had apparently balanced translocations and we were working out how we could use the flow cytometer to karyotype patients. When we came to Cambridge I advertised for somebody to come to work our new dual laser flow cytometer and, to cut a long story short, we hired Nigel Carter. Nigel Carter was working on the flow cytometer that Peter Morris was using in Oxford to separate pancreatic cells in a diabetes project. Nigel was getting fed up with doing this and was quite intrigued by the possibilities of chromosome sorting although he didn't know anything about chromosomes. We started sorting translocations onto filter papers and using radioactive probes to map specific loci onto these spots on the filters. We had both derivative chromosomes and had to see which part of the chromosome carried the locus that we were interested in. Our major effort was to map chromosome 9 using this method. While we were doing this, a chap called Hakon Telenius was working upstairs on developing a random primer for DNA amplification. So we thought it would be a good idea to test this out on chromosomes. We random primed sorted chromosomes and then of course labelled them with the fluorescent nucleotides that we were using at the time for the in-situ work. We showed that you could make chromosome paints for identifying abnormal chromosomes. We sorted and labelled abnormal chromosomes and then painted them back onto normal metaphases which revealed the origins of the translocated chromosomes. This was the new reverse painting method for analysing chromosome aberrations and you published this in the Journal of Medical Genetics.

PSH. Yes

MFS. Were you Editor at the time?

PSH. I was.

MFS. And that was published in '92. Then in 1993 I was joined by Fengtang Yang. Yang knew about this sorting and had applied to come to me but I hadn't a place at the time. So he went to Glasgow first and worked with Liz Boyd and found that nobody was using the sorting machine. So he asked again if he could come to Cambridge to join my group. He had been studying the phylogeny of Muntjacs. The Indian Muntjac had the advantage of only having 3 pairs of chromosomes and we had two probe colours at that time. We painted one chromosome red, one chromosome green and the other a mixture that fluoresced yellow. This produced the most beautiful pictures of chromosome territories in nuclei. I don't know what possessed me but we never published this till much later. This was in '93 but I used the images in lots of lectures and people were intrigued. I am convinced that this started everybody looking at chromosome territories in interphase nucleii. Anyway, Yang painted the black muntjac, the Gongshang muntjac and the Chinese muntjac with chromosome specific paints from the Indian muntjac and revealed new information about karyotype evolution. We got more samples from the brown brocket deer and the water deer of China and various other types of deer including the reindeer and the red deer. Yang worked out that the Indian muntjac chromosomes were composed of fusions between the chromosomes from an ancestor with 70 different chromosomes. You could see them just one after the other, head to tail, all the way down each chromosome.

PSH. That's amazing.

MFS. Not only that, but when you use a probe for the centromeric repeats you can see fragments of the ancestral centromeres in between each pair of these tandem series of ancestral chromosomes. So I got really excited about this way of looking at evolution. Yang has now been with me for ten years and we have studied over 100 different species from which we have made chromosome specific probes, to work out the phylogeny of mammalian orders and families of mammals. For example, we resolved the proper karyotype of the dog, which has 78 acrocentric chromosomes that are very difficult to distinguish, and we tied up each chromosome with known genetic linkage groups and this helped to map the dog karyotype. Using the dog we have determined karyotype evolution in carnivores and have worked out the phylogeny for horses, zebras and rhinocerouses etc.

PSH. And marsupials?

MFS. Willem Rens in our group has been doing the same thing with Australian and South American marsupials. He and I are working on the monotremes at the moment. We have got beautiful preparations on platypus and, in the last two or three weeks, on echidna. We discovered that these monotremes have unique sex chromosomes, in fact a whole chain of

chromosomes instead of just the X and Y; the male platypus has 5 Xs and 5 Ys and the echidna has 5 Xs and 4 Ys.. Anyway, we're trying to work out how this has evolved.. It's very difficult. Recently we have worked on birds, including the chicken. The chicken is very well mapped now. The homology between humans and chickens is quite well done and for example we have looked for the sex chromosomes in crocodiles and turtles, because these are animals that have temperature sex determination. We have found that the Z chromosome from birds paints one pair of chromosomes in both turtle and crocodile without re-arrangement. We want to work out the comparative map of turtles and crocodiles from chicken. Human to chicken homology is available from gene mapping and so it is possible to transfer the information from human to crocodiles. Of course these are the relatives of the dinosaurs and take us way back. So that's exciting.

There is another theory that Yang has been involved in, namely the presumptive ancestral karyotype of all mammals. There's a group of animals that don't look in the least bit like one another, i.e. the aardvark, the tenrec, the elephant, the golden mole, the hyrax and the manatee. They are all morphologically different of course, but they have very similar genomes in terms of the molecular sequence of various genes. A theory has developed that they represent the most basal clade of animals which came out of Africa. We find that their chromosome homology maps are similar and close to the proposed mammalian ancestral karyotype.

PSH. This is fascinating.

MFS. This has been achieved by painting human chromosome specific DNA to the chromosomes of all these different species and constructing homology maps indicating particular patterns of homology. For example, human chromosome 14 and 15 are associated together in the chromosomes of most animals. Chromosome 3 and chromosome 21 are also present in one block in almost all the animals that we know about. Using this approach we can construct a karyotype that contains all these primitive associations. The work is basic and nothing much to do with Medical Genetics. When I left clinical work and left directing the Clinical Genetics Service, and left being Head of Pathology, I wondered what I could usefully do. I had been interested in the vet school for quite a while and I could see that we might apply to veterinary medicine what we had been doing in human genetics; there was a tremendous lot of animal material to be exploited. One of our students here is working on sarcoma in dogs, learning what are the important genes involved. We are looking at the cytogenetics of sex reversed cats and horses and the offspring of mules. The mule study has given unique results. There are a few mules that have actually given birth and we have samples from mule offspring from Morocco, from San Diego and from China. We have studied all these using horse and donkey probes and have discovered that there are two types of fertile mules. One particular type was found in which the offspring of the fertile mule has the complete maternal horse set from the mule and a complete set of donkey chromosomes from its jackass father. The other class is quite different. They have a combination of translocations between horse and donkey from the mule parent, plus some chromosomes consisting of both members of either horse or donkey chromosome pairs.

This seems quite remarkable in a living animal. Anyway, that should be published shortly we hope

PSH. Well Malcolm there is plenty to keep you active.

MFS. I think it is important to try and keep your mind active and to do something you are enthusiastic about.

PSH. It's nice to come back to something you can be directly involved with yourself too.

MFS. I had great ideas of getting into the lab and using a pipette and so on, but it hasn't actually happened yet.

PSH. No but you are involved in the concepts.

MFS. And writing and figuring out how to plan the work. You might be interested to know how we finance the work. Some of it is run out of what we earn from distributing human and mouse paint probes around the world. Also, I now have a Wellcome Trust Programme Grant to provide DNA from other species free of charge to anybody who wants it. As a result, we have collaborations all around the world providing chromosome specific DNA to scientists from their favourite species. We call ourselves the Cambridge Resource Centre for Comparative Genomics and we have a special web site. The grant pays for a couple of technicians and half of Trish's salary and a post doc but the rest are paid from what we earn. The reason I got into marketing the paints was that once we started sorting these chromosomes in 1992 everybody wanted to use them. The result was that my technicians were so busy sending the stuff out to all our friends that they weren't doing anything else. So I was complaining about this to a local entrepreneur, Dr Peter Dean, who runs a firm called Cambio who offered to help. If we made the stuff his firm would put them in boxes and send them out to people. That now brings in a very good return every year out of which we pay the technicians and the University for allowing us to use their facilities.

PSH. Malcolm are there any other things that you want to kind of go over or bring up that I haven't mentioned?

MFS. I think you must be getting tired of this by now. It's ten to one.

PSH. I think we should draw it to a close.

MFS. I might mention briefly two other areas before we close. One is prenatal screening and non-invasive testing for Down's syndrome. The other is the development of the genetic network system in Scotland and here in East Anglia. In Scotland I set up the Genetics Consortium….

PSH. Which is still flourishing.

MFS. It still flourishes yes but it took longer to happen in England.

PSH. At last.

MFS. It's taken a long time. Like you and Rodney Harris, I was concerned about trying to maintain our network through the Margaret Thatcher years. I feel that this is one of the greatest strengths of our system that we are able to work together, to share resources and to give a proper service to families even though they were widely spread out over the country. I appreciate that we only helped a tiny proportion of the population that needed our help and that is still the case I am afraid.

PSH. But still we saved that network through those difficult years.

MFS. We saved it. When I came to Cambridge, it was the only place in the country that didn't do prenatal screening and I had a lot of persuading to do to get it started. It is ironic that Spencer Haggard, one of the public health officers responsible for services in East Anglia had been a PhD student with me in 1973. He wrote a good thesis on the cost-benefit analysis of programmes for prenatal diagnosis of Down syndrome. Cedric Carter was his external examiner. I had hoped that someone like him from public health, trained in genetic testing, would help promote genetic services in the community. But Spencer did not take this opportunity. The result was that prenatal screening had to await my arrival in 1987.

PSH. Yes

MFS. It was a disappointment to me.

PSH. Never mind. Just to finish, I mean is it fair to say that if you look back and ask which area of your work do you really feel most proud of, that you feel you have made a special contribution to above all the rest, what would you choose?

MS On the research side, I would choose the work on Turner's syndrome and the XX males; the latter pointed the way to discovering the testis determining gene in man and all mammals. But the most useful work was undoubtedly the development of genetic services in Scotland.

PSH. And the Klinefelter work?

MFS. It was planned as an MD thesis but I made the great mistake of burying all my Klinefelter work in a chapter in a book in 1966 called the Sex Chromatin. It is a most comprehensive account of Klinefelter's syndrome but I regret that I didn't publish it in a proper journal.

PSH. Malcolm thank you very much and well I think – let me stop the machine. **(end of tape)**