

Maj Hulten

Personal Details

Name	Maj Hulten
Place of Birth	Stockholm, Sweden
Main work places	Stockholm, Sweden; Birmingham, UK
Principal field of work	Human cytogenetics

Interview

Recorded interview made	Yes
Interviewer	Peter Harper
Date of Interview	25/05/2004
Edited transcript available	See Below

INTERVIEW WITH PROFESSOR MAJ A HULTEN, 25 MAY 2004

PH = Interviewer (Peter Harper)

MH = Maj Hulten

PH I am interviewing Professor Maj Hulten at her home in Moseley, Birmingham and it is 25 May 2004. Maj, can I ask first, how did you come to have a career in science in the first place?

MH I was initially interested in psychology and I started at the University of Stockholm in 1952, taking courses in psychology, in education, and at that time there was a lot of physiology in psychology, not only differential psychology which was lots and lots and lots of mathematics which I learned by heart, and I had a great appetite, intellectual appetite, so I learnt all of these things, which are completely useless, by heart. But in physiology I got very interested in various aspects of physiology, so I asked if I could study physiology at the Wennergren Institute in Stockholm in the Zoology course. And, miraculously they accepted me to do that. And in that course I read one sentence, which said that by apparently pure DNA it had been possible to transfer genetic characteristics from one strain of bacteria to another, and that just threw me and I thought, oh I must study genetics.

PH Was that the work of Griffiths I suppose?

MH I don't know. This was probably in 1954 sometime, so it was an older observation. It wasn't new, but to me it was completely new. Then I also went on a Marine Course in the southern part of Sweden and that was very exciting, so I decided that I would like to study Genetics. Now at that time you had to have full exams in both Zoology and Botany in order to be allowed to study Genetics.

PH Am I right your father was Professor of Botany?

MH Yes, he was.

PH Was that in Stockholm?

MH Yes, first he was in Lund and then he became a Professor of Botany in Stockholm at what is called the Natural Historical Museum, and he was interested in the spreading of plants, in particular circumpolar plants.

PH Did you have an interest yourself in plants and animals and wildlife?

MH I was most discouraged, because he was a very autocratic man, and he somehow thought that the Latin names of plants would be inherited, so he was very upset when I didn't know the Latin names of plants and I was totally discouraged by any thought of more systematic investigation of plants; and so I said, I can't study Botany and neither was I very interested in studying Zoology. I managed to get on the Genetics Course in spite of not having exams in either Botany or Zoology. I asked the Professor of Genetics, Professor Bonnier "Could I take Genetics?" and he said "No". Well, I said "I want to study Genetics" and then I suggested that if I come first in the Entrance Exam, would you take me and he said "Yes".

PH And this is Stockholm?

MH This is in Stockholm, Stockholm University now, and then I just locked myself in and spent, oh a long time, reading and learning Müntzing's book on Genetics.

PH When was it published?

MH Oh it was a couple of editions. I think I have mentioned that in this little thing I wrote for Cytogenetics and Genome Research (1).

PH I can check that out. Would I be right in assuming that really, Genetics was well advanced in Sweden, because to have a course, a University Course fully in Genetics . . .

MH But this was only Drosophila Genetics.

PH OK.

MH It was only Drosophila Genetics. Nothing else, and Bonnier was the first to organise such a Course. Of course I have not followed up what Bonnier did, I don't remember that. But he was then succeeded by Lünig and the other person who was there was Claes Ramel, who is still alive and still working, and he might well be a good person to interview about the early days in Sweden.

PH So you went into the Genetics Course. Was it a 3 or 4 year course, or was it just part of something with Zoology and other subjects?

MH No, no, no. Genetics was a discipline, a full course. I can't remember, two years at least. And then, this was a crazy time because we studied so hard, I mean it was totally different from what I think it is nowadays. But anyway I said I didn't want to push flies around. I didn't like to anaesthetise Drosophila flies. They are lovely, lovely creatures and they are extraordinary as regards what you can learn from studying them but I was fascinated by chromosomes, although then the only chromosomes we could see was the, what are they called?

PH The salivary gland? Giant salivary chromosomes.

MH With their bands but I wanted to study human chromosomes.

PH Can I ask you, because I am very ignorant about much of cytogenetics, in your course in Stockholm, were those chromosomes the only things which the microscopy could show or was there well developed microscopy of what you might call ordinary chromosomes?

MH As far as I am aware we could not by microscopy study any other chromosomes but the giant salivary ones. We learnt of course Human Genetics and the textbook Principles of Human Genetics was by Curt Stern, in German.

PH Yes. That was already published by then was it?

MH Yes. In German and that was basic genetics theory, but there was also a lot of plant genetics. The Institute was concentrating, focusing on Drosophila, but the course was very wide and I was absolutely fascinated by evolution, by all the stuff that we had to learn then. The Mendelian revolution was also something, which I was really taken by; I can't remember all of the text books that we had but one of them was Dobzhansky and the Human Genetics was just characters, phenotypic patterns of inheritance.

PH So when was it then you went over to Lund? Was this 1955?

MH '55. In the autumn '55.

PH And this was for a 3 or 4 month project?

MH Yes.

PH So you just hit the critical timing in terms of Tjio and Levan's work I suppose.

MH Yes. I don't know much about the background but of course Tjio and Levan have had very different views of what actually happened.

PH I know. And am I right though that, whereas you had hoped to study human chromosomes yourself, Levan suggested something different?

MH Well, when I first met Levan he suggested that I would look at mice and look at the ascites tumours, and I would look at the effect of X-irradiation on them because they had found previously that

hydroxy-quinoline led to something which they called C metaphases, and he was wondering whether the same thing would happen after X-irradiation, so that is what my project was.

PH Am I right that Levan had been collaborating with America very extensively on the cancer cytogenetics ?

MH Oh yes, he had just come back I think from a long visit in the States and had done lots and lots of attempts, I understand later, lots of attempts in getting chromosome preparations from, well, some from human chromosomes as well.

PH Which centre was it and who were the people he was working with?

MH Theodor Hauszka was it?

PH I don't know.

MH What I can give you is, or what I can translate, I have actually got from Karl Fredga a historical account, which Albert Levan has written himself in Swedish, which was never published.

PH That would be hugely interesting.

MH And that describes, that is basically a defence against Hin Tjio's attacks that Albert Levan didn't have anything to do with the project on human chromosomes, so he wrote this I think for a paper by the Svenska Forschningsthat is the Swedish Research Association. They had a paper and, as I said, that has not been published and I have got that. And in that he gives a very detailed account of what he did.

PH Can you tell me, at the Institute in Lund was the standard of equipment and microscopes very high? The reason I ask is that, in Paris they had very primitive microscopes and I get the impression talking to others that one of the reasons why Sweden contributed so much was that it had this very high standard of microscopes.

MH I don't think so. If I look at the pictures I took of the ascitic tumours, I mean they are quite blurred by comparison and you can see that the preparations, we made squash preparations always at that time, hypotonic pre-treatment and squash preparations, but my memory is not that we had any absolutely phenomenal microscopes. I think we could look at that, because I think there are pictures of Albert Levan with the same type of microscope as what Hin Tjio did have, and I probably had as well, that had a camera attached to the microscope, but Levan did the camera lucida drawings and didn't think it was a good thing to photograph. I don't understand that.

PH Did you have to do drawings of chromosomes?

MH No, I never did. He said I should. He said it was the only way of making good observations, with the camera lucida, but he was the only one who did that at the time. Nobody else.

PH What about your own project? How did it go, that project that you did?

MH Oh very well. Very well. I found some very interesting things of the chromosome behaviour after X-irradiation but I never published that. Possibly because I was shy I think, and I would like to find the write up. That would be nice, but it must be there somewhere, but on the other hand the one other person you might want to talk to is Albert's son of course, Albert Levan's son, because he has got the whole collection of Albert's reprints, which he doesn't know what to do with.

PH Am I right he is in Göteborg.

MH Yes he is.

PH He is medical?

MH He is a Professor of Medical Genetics.

PH In Göteborg?

MH Yes. Cancer Genetics.

PH In Cancer Genetics, right.

MH I think he is a professor. He is a full professor in Genetics. But his main interest is Cancer Genetics.

PH Well that's something I'm ignorant of.

MH Very nice. Very nice chap. So I was very sorry to hear that he didn't know what to do with his father's collection and I think he would be very pleased to give it to somebody.

PH Well, I must write and perhaps try to see him when I'm in Sweden.

MH Yes.

PH Did your own project then get published as a thesis, or were they . . . ?

MH No, it was just a little thing. Not at that time, no. It was just a little thing that was written up. I don't have a copy and I'd like to see what I did write because when I came back and I was explaining what I had seen, I got some very starved chromosomes, which were very thin, and I speculated how this could come about and when I came back to Stockholm and it was read by KG Lünig he said DNA. What? DNA? I don't know why. I had speculated something and he was dismissing what I was trying to say.

PH I suppose this was only 2 or 3 years after the Watson-Crick paper.

MH Oh well, sure.

PH And even Watson and Crick put it forward as a hypothesis so I suppose. . .

MH Well Watson and Crick was '53 wasn't it, so they were talking about '56 now, '55 probably yes. Alright then. But I thought that....

PH You were convinced

MH I thought it was really funny. KG Lünig is still alive and is very active, so you have a lot of people you can interview in Sweden.

PH Just coming back to that time, and I know you have spoken and written about it elsewhere [1], but it is a very interesting time, the end of 1955. When did you first run into Hin Tjio?

MH The first time I spoke to him was on that, what I think must have been the night before Christmas Eve, when he was catching up with me in this culvert, underpass. Which I don't know, I can't remember that underpass, but anyway I had probably seen him but I had never spoken to him before.

PH Do you think that he was interested in sharing the findings with you because perhaps you were a student and not likely to be any threat, or do you think he was just wanting to be sociable.

MH No, I don't know. No. I mean he had actually showed it to Karl Larsson before, which he told me. I think he was just so excited, and I don't think anybody else was around at that time in the middle of the night. And of course, it could be that I was not a threatening figure. Now Levan wasn't away at the time, as I might have indicated. He was just not there, because it was Christmas time and also because Hin would never in his wildest imagination want to show Albert his results.

PH Had Hin been in Lund for a year or so?

MH Oh no no.

PH Because he was in Sweden?

- MH Only a couple of months I think. He describes in his 'Obstetrics and Gynaecology' paper that Rune Grubb asked him to come urgently. I don't know about this.
- PH So do you feel at all that Hin Tjio had already developed the work in Spain before going to Sweden or . .**
- MH No. No. No.
- PH He couldn't really have.**
- MH No, under no circumstances.
- PH So it must have happened very quickly, just in a few months?**
- MH If you have cells, fetal lung fibroblasts that grow like grass, and then you just expose them to colchicine for a couple of hours to arrest cells in metaphase, then expose them to a hypotonic solution to spread the chromosomes and fix them with acetic-orcein, make squash preparations and they are ready for microscopy.
- PH But I could imagine, perhaps as not being a cytogeneticist, that the whole process might take quite a bit of preparation. The setting up of the cultures and the techniques.**
- MH No. Rune Grubb was growing them, for what reason I don't know, and I don't know who negotiated that they would be transferred to the Genetics Department, and that is where we don't know whether this was Albert Levan or Hin Tjio, but anyway I don't think it would take a lot of time. All you need to do is to have the culture flask and expose the cells to colchicine, a hypotonic solution and acetic orcein, and then make squash preparations, which T. C. Hsu had developed before, and so the recipe was there already, and of course Hin tried various concentrations but I don't think he had been trying very long.
- PH Did you get the feeling then that the photographs that he showed you . . .**
- MH It wasn't photographs.
- PH Was it directly down the microscope?**
- MH Oh yes, at the time there were no photographs.
- PH So did you get the feeling that that preparation was really the first time that he or anybody had seen the correct number, or ...**
- MH Sure. I had not seen the ones by Melander and Melander so ...
- PH But I was thinking of Hin's own work. I was wondering whether he might have had some trial runs and then felt he needed to have a further set to confirm his findings, but you think this was as it happened?**
- MH Oh yes.
- PH From what you've said and from what he's written it sounded like, it happened at that very precise time and on that date.**
- MH Oh yes, I am convinced. I am convinced that there were not enormous disappointments. I would have thought that that is what happened to Albert Levan.
- PH Yes.**
- MH And why, I think the reason for that was that he was not looking at normal tissues. He was looking at cancers, where you don't know whether, even if you have got chromosomes well spread, you don't know whether it is normal or not, as cancer tissues show many different kinds of chromosome abnormalities. So I would have thought that Albert Levan had equally good preparations, and had he

had the good chance or good fortune to have somebody, who had given him good normal material, such as fetal lung fibroblasts, in the States, he would have done it for himself.

PH Yes

MH I don't think there is any magic here.

PH Did Levan know that Tjio was working on human chromosomes?

MH Absolutely. It was a joint project. It was, although Levan never said anything to me, but my understanding was that it was a joint project because Tjio never worked with anybody else in Lund. He was always collaborating with Levan, and although he pretends that he got the cell cultures directly from Rune Grubb by the initiative of Carl Larsson, I doubt whether that is correct, I don't know, but I am doubtful whether that is correct. I would have thought that it was more that it came about with lots of different initiatives, and Levan asked him to come as he usually would do and then they made out that Hin would do it and so forth. I don't think this was some initiative from Hin Tjio or done independently, however much he has been claiming that, I don't think so.

PH I get the feeling from what I have read and from what people have told me that Hin Tjio was a very driven person, and very intense; am I right that he really worked day and night, or at least night?

MH Well he was practically monomaniac. He was married to a woman from Iceland who lived in Copenhagen at the time and he would very rarely go over to Copenhagen. He did nothing but work. And he would only communicate with some people and very intensively. Very intensively. He was a close friend with many people and totally ignored everybody else. And then he had some certain enemies. But he also had some really curious ideas, that he was looked down upon being Chinese, for reasons which are absolutely, totally unclear. I spent hours and hours and hours and hours and hours trying to say that's rubbish to him. How can you think something like that. And he just came back and came back and came back and said "I'm sure you look down upon me because I am Asiatic".

PH Yes. Maybe his war time experiences gave some of his problems.

MH Could be.

PH Because I gather these were quite horrific both during the war and....

MH I don't know much about it, except for that he had a bleeding heart for everybody suffering. A very unusual man. But how he could get that idea, I mean for heaven's sake. The Japanese are also . . .

PH Am I right that in the Lund laboratory at the time, most of the research started in the evening because of the teaching in the day?

MH I don't know if that is right for everybody. I am sure there were fractions of different types but there were, for instance, there were people who were never there in the evenings including Müntzing. Müntzing was a sort of 9-5 worker as far as I am aware. Very well respected by everybody. Very distinct and very learned chap. The Melanders would never be there, not late at night anyway. Then there were some people, among those was Gunnar Östergren and his protégé Theresa Wakonig, who I don't know where she is and I have never found any publications from. It was Yngve Larsson who was the Human Geneticist, who complained that he had no tools except for enzymes and stuff like that. And he very often came and stood in the door and he believed that I was doing cancer cytogenetics, so he would come in and stand in the door, and he would say 'we are writing cancer history'. Get lost! And then there was Hooda Zogby and Einar Vigfuson from Iceland and a couple of other people. But there were other people, who worked there, who were more daytimers, Dieter von Wettstein for example. I never saw him in an evening.

PH And was the main activity of the lab centred around cancer cytogenetics?

MH No. No. It was primarily plants. So this was a little pocket of Levan, and Levan had at the time no pupils.

PH So he was not Head of Department at that time?

MH No no no. Müntzing was the head of department. And Levan had, I don't know, but I think I was the only one and then he formed the cancer research lab, but I wasn't aware of that and I believe that must have been later, but I could be wrong.

PH Quite a lot of his work, am I right, was on Allium?

MH No, that was earlier. The Allium test, that was before he was interested in cancer, but then of course, later, the cytogenetics exploded in the Genetics Institute but in 1955, the beginning of 1955, there was only himself and Hin, and as far as I know, no other people doing cytogenetics. Oh Melanders of course, but they were totally separate for reasons which I am not at all clear about; the Melanders never spoke to Albert Levan, and I heard rumours that they were trying to sort out Klinefelter's and I remember once I asked, I knocked on their door and I wanted to see their preparations, but I can't remember more. I remember the microscope and how they were sitting, but I can't remember the images.

PH It's unusual to have a husband and wife team working on the same project like this. Were they there as graduate students or as faculty members?

MH No No. I thought they were members of staff. But they were interested in, I think they were interested in rabbits, but what they have published I don't know.

PH Yes. You said people called them the rabbit people.

MH Oh we did. We called them the rabbit people and I believe that they also tried, but I am absolutely positive that they tried to look at Klinefelter's but what tissues they used I don't know, because I don't understand what tissues they would use at that time.

PH It could only be bone marrow.

MH Yes but . . .

PH That wouldn't have been easy.

MH Well it would have been easy if you had a good sample. I also have a vague idea they were trying Turner's as well but I don't know. But they were totally isolated, that I am sure about.

PH Can I ask you one question about Hin Tjio which has puzzled me? After he went to America he really didn't publish very much in the way of major original work and he didn't stay in Denver very long. Have you any idea why he didn't really do so much more, or do you think it was his personality made things difficult or . . .?

MH I have no idea. I have no idea why. Maybe he couldn't get the type of material, or he wasn't having the overview, or he got interested in – I don't know, I didn't follow very much what he did at that time. Do you remember what he was actually doing? I think I have written about that but I have forgotten now what he actually did, immunity?

PH I think it was.

MH But I mean he was in a place where there was no human material.

PH Yes.

MH So he probably was as you say, isolated from possible sources.

MH And no clinic, not like being in Edinburgh, where people like Pat Jacobs and David Harnden had all of these.

PH Absolutely. Yes. Can I come back now Maj, to your own work. After you did your project in Lund then you went back to Stockholm, did you do a PhD after your degree, or how did things develop?

MH Well No. What happened was that I decided to study Medicine on that very day when Hin showed me those chromosomes because I thought, golly this will be the idea, the idea that there may be trisomies and monosomies, deletions, duplications, inversions, insertions and all of this in the human just threw me about. So I left Genetics and went into Medicine in Lund first. That took a couple of years to take my Bachelor in Medicine.

PH It must have been more than a couple of years perhaps, would it have been?

MH Three years.

PH Three years.

MH In Sweden it takes three years, and I hated it from the beginning to the end. It was taught in a very dry way. Anyway, so then I decided to move back to Stockholm and studied Medicine for a couple of years in Stockholm, and then suddenly Jan Lindsten rang me and asked me if I would like to come to his department, and I stopped in the middle of my medical education and I said OK then. And I came there in '63.

PH Am I right that in the Swedish system you can do your Bachelor of Medicine degree and then, if you don't want to continue in practice you can, so to speak, move laterally into other things.

MH Yes, but that wasn't my idea. I wanted to become a doctor.

PH You went on to complete in Stockholm your medical studies and . . .?

MH No I interrupted my medical studies, because I was so attracted by the idea that somebody asked me to do Medical Genetics and Cytogenetics, and that was horrendous because it was only me, Lindsten and two half time technicians and I had to run the lab and do all the ambitious things that Lindsten wanted to do, and I was a slave from '63 to '74.

PH When did Lindsten move from Uppsala to Stockholm?

MH I think it was sometime before. I don't remember when but certainly in '63 we were located in Endocrinology, and Lindsten and I were sitting in the same room and I did all kinds of things. I ran the lab. And Lindsten had already done his thesis on Turner's syndrome, and he was very ambitious and worked with Marco Fraccaro a lot.

PH Was the lab set up as a Medical Cytogenetics...?

MH Service lab. Yes.

PH Even at that stage? Part of the hospital, was it?

MH Yes, at the Department of Endocrinology.

PH That's interesting. It must have been . . .

MH The first one.

PH I was thinking the first probably in the world to be a Service lab, just about.

MH Maybe.

PH That's interesting, because so much of the early human cytogenetics was done by people working in a more basic research environment. So what kind of work was there? Was it diagnostic samples or were you allowed . . .?

MH Diagnostic samples, lots and lots and lots of diagnostic samples. No banding. No banding at the time, so we just tried our very best, and of course we missed lots and lots of things. During the time I was

there, Lindsten built up the lab with more and more and more people, and I started trying to do my meiotic work in '65, and then I had a few exams to do to get my Med. Lic. I had done my clinical part, so I only had some more exams to do.

PH So what was the first piece of meiotic work that you did?

MH The very first piece was a translocation carrier, where I had a testicular biopsy sample, and I was working at night with the preparations I had made, which I had made by a modification of the same technique that we do for blood chromosomes. I couldn't see anything and I threw them in the bin. I was really upset and then I came back the next morning before the cleaners, and I fished them out again and I found some translocation quadrivalents. I had nice preparations and I had spread the chromosomes so well and I was looking with, not the confocal microscope, but just by taking down the condenser so you get to see a bit more, I hadn't stained them with anything, so they were quite difficult to see and I was probably tired, so it was good luck that I saw the translocation quadrivalents there very clearly in the first metaphases. We thought at the time that that would locate the Kidd blood group, and we published this in a little paper, in Lancet, no in Nature, a little letter to Nature in '66. It became later clear that it was all, the main aim of the exercise was to publish something, and I believe Marco Fraccaro was also on the paper, that we had found this gene, which was not. All I did was the chromosome preparations.

PH I always get the feeling that the people working on meiotic problems are almost a distinct subgroup of cytogeneticists, at least those people who make it their main research area. Perhaps I am wrong.

MH Well, I don't know who you mean really, but there are quite a few people who had been having a touch and go with meiosis.

PH I was thinking perhaps of people like Ann Chandley, in Edinburgh; it is perhaps because I know rather little about the practicalities of meiotic work. It always seems to be a very...

MH It is very frustrating, very frustrating, but at the time it has been very frustrating because of the fact that you have to have gonadal tissues, either testicular biopsies and now also fetal oocytes, in order to look at recombination, crossovers, which is most interesting as far as I am concerned. But now there are very many more people, some more people coming along because of the new technology. There are so few human. There are very few. Why have I persevered? Because I think it is such a basic thing and we know so little.

PH Can I ask, when did you start to get the idea of using meiotic techniques for gene mapping? You mentioned . . .

MH No no. That wasn't mine. That wasn't my interest at all.

PH But in terms of . . .

MH And I haven't mapped a single gene.

PH I was thinking more in terms of the more general meiotic distances.

MH Oh, you mean recombination.

PH Yes.

MH So, that was very obvious, that by looking at crossover distribution, chiasmata distribution, you can make genetic maps.

PH Had you started to do that already during your time in Sweden or was it mainly when you came over to this country?

MH Oh no. I made most of the work, most of the stuff that is still valid, I started probably in '67. In '71 I had done quite a lot. In '70 I got hold of the Q banding, and that allowed me to measure the chiasma

positions on individual chromosomes. Then I learned about C banding, which allowed me to pinpoint the centromeres and the position of the chromosome arms. So I had done all of that by '71 when the Paris meeting was, and I put all the data actually into this little leaflet, what is it called?

PH It was the Paris Human Genetics Congress.

MH There is a little leaflet where I put in all my basic data and then I published in '74. I had a dual interest. I realised this would be interesting for genetic maps, but the point is nobody believed it, because everybody thought that when a chiasma is formed where the crossovers take place, that the chiasmata would move from their original positions towards the end of the chromosomes. This is a daft idea and I was sort of discouraged by everybody, and probably I didn't make the most of it, but it is interesting now that the most recent maps that have been done by linkage are nearly exactly the same as that old work.

PH What year was it Maj that you came over to work in England.

MH '74.

PH '74 and who was the link that made you come over?

MH Well, I had struggled between '66 and '74 to get my PhD together, and when that was finished I wanted to continue in Genetics, but there were no jobs in Sweden.

PH Right.

MH Because the only lab that existed was in Stockholm and there were no jobs, I mean at least no research jobs.

PH So you would have had to stay doing a diagnostic post?

MH Well, I went out as a school doctor, I don't know what you call that.

PH Yes.

MH And I found that the most boring thing I have ever done, checking healthy kids. I like kids but it was extremely boring. So then I decided this is not for me and I worked as a psychiatrist for a while but I wanted to continue in Genetics, so then I took up one Lancet issue and there was a job advertised in Leicester as a . . . Well I applied for that job and I asked Malcolm Ferguson-Smith if he would be my referee. (telephone rings – pause).

[The end of the recording is missing due to a technical problem]