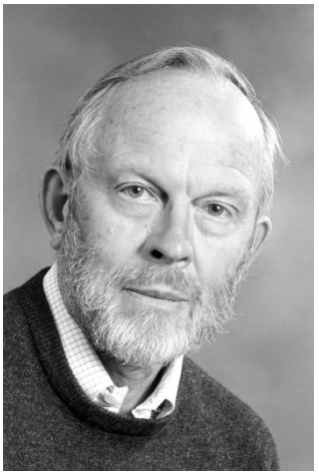
Newton Morton



Personal Details

Name	Newton Morton
Dates	Born 1929
Place of Birth	Philadelphia
Main work places	Madison, Honolulu, New York, Southampton
Principal field of work	Mathematical genetics, human gene mapping
Short biography	See below

Interview

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

Personal Scientific Records

Significant Record set exists

Records catalogued

Permanent place of archive

Summary of archive

Biography

Newton Morton was born in Philadelphia and educated at University of Hawaii, Honolulu, receiving his BA in Zoology in 1951, followed by a Masters degree, and PhD in Genetics from University of Wisconsin, Madison. From 1952 – 3 he worked as geneticist to the Atomic Bomb Casualty Commission. After faculty positions at Madison he became Professor at University of Hawaii in 1962, remaining as Director of the Population Genetics Laboratory there until 1985.

After two years as Head of the Department of Epidemiology and Biostatistics at Sloan-Kettering cancer Centre, New York, he moved to Britain in 1987 as Director of the Cancer Research Campaign Research Group in Genetic Epidemiology; Southampton University, where he remains Senior Professional Fellow in Human Genetics. His principal contributions have been in the fields of human genetic linkage analysis and broadly in genetic epidemiology.

INTERVIEW WITH PROFESSOR NEWTON MORTON, 14th MARCH, 2005

PSH. It's Monday 14 March 2005 and I'm talking with Professor Newton Morton at Southampton General Hospital, Southampton. Newton. Can I start at the beginning and ask, whereabouts were you brought up?

NM. I grew up in Connecticut and left at age 18 and then, through a series of accidents more or less, I spent some time in Hawaii and went to Wisconsin for graduate work, to Japan and so on. So I actually lived more time in Hawaii than anywhere else, single place in America.

PSH. Can I ask, did you come from a family with a medical or scientific interest that might have started you in this direction?

NM. Not at all. My father was very much interested in and worked in transportation, in Pennsylvania, the railway, but then during the war he became an instructor in transportation at Yale. When the war was over, he decided he liked it so much that he went to Kent State University in Ohio and spent the rest of his life teaching, so it wasn't that. I got interested through collecting butterflies primarily, as a small child, and I thought I wanted to become an entomologist, but I realised when I took a delightful course as I suppose a freshman or sophomore, that while I loved it I didn't want to make a career of it. And I got very depressed and I went into the biology library at a time when a small library could have everything of consequence, and came across Dobzhansky and Ernst Mayr and Simpson, and spent about two weeks there just reading furiously, looking for something to replace entomology, and it was quite clear that population genetics was for me exactly the right thing. Tremendously influenced by Dobzhansky's book and then it was easy after that.

PSH. It always intrigues me how many people in genetics have started interested in either butterflies, or at least with a very strong interest in natural history

NM. You see that's gone. That was true for Pat as well. She was into botany.

PSH. She told me.

NM. But nowadays into computers. It is a completely different world. It's a non- living world.

PSH. I wonder sometimes if that's coming back a bit.

NM. I hope so.

PSH. I get the feeling there is a renaissance of what you might call whole animal field study.

NM. It tends to take the form I think of wildlife biology, which involves protection of animals and things like that. My second son is a wildlife biologist in Alaska and it's a mixture. I ask him sometimes, is he representing the

animals or the hunters or the walkers or the campers or. He agrees it's a problem.

PSH. So your first degree, which university was that, Ohio?

NM. It was Hawaii.

PSH. Oh it was Hawaii. How come you got to university at Hawaii?

NM. Well it was a combination of two things, first I married young to a girl from Hawaii, secondly insular speciation was a very popular subject at that time and I thought, what a great opportunity. It's just like Darwin and the Galapagos. The [Drepanids]were not there but the Drosophila were, and I was fortunate in having really an excellent genetics course in Hawaii, which just made me feel much more certain that's what I wanted to do, and of course in those days it was heavily algebraic, and I liked that combination of living things. I had not thought of human genetics at all as a career and people didn't in those days. I think, several years later Josh Lederberg of Wisconsin was very concerned that I was going to intercalate a year and a half in Japan for the Atomic Bomb Casualty Commission, and was developing an interest in human genetics, because he felt that I would be lost to genetics.

PSH. I am interested that, back at that early stage you obviously had a leaning towards mathematical quantitative analysis, because some people do and some people don't, and that must have come out pretty early.

NM. Well it was for me lucky that it was a time when that was a very important part of genetics, in some sense it is not in the same way to people who have a mathematical leaning tend to come in from statistics, much more, rather than from biology. It's changed the flavour of genetics a lot.

PSH. Can I ask, who was in charge of the genetics teaching and work in Hawaii at the time when you went as an undergraduate?

NM. There was a chap who didn't realise his potential. He had enormous influence over me. He had done his graduate work at Texas with Patterson and that lot, and a contemporary was a chap he recommended to me to do graduate work and clearly to work with Drosophila, and that was Jim Crow at Wisconsin. I also had the idea, I think he suggested it, of Curt Stern in Berkeley and I tremendously admired him, but in retrospect my algebraic leaning was much better served by going with Crow.

PSH. What year was it you graduated in Hawaii.

NM. It would have been '51.

PSH. And then did you go from there to Wisconsin?

NM. Yes

PSH. And how long were you there?

NM. Well at that time, I was there, and that interval was actually just one year, because I arrived from Hawaii in February and went to see Crow, who I'd never met before, and we chatted about this and that. I remember the housing we could find right after the war was very poor. And he said, get settled, don't make any decisions. Well, I'm interested in any projects. I think would make a good Masters. He said well, there are few I have had in mind and he named 4 or 5 and I said I want number 3 if that's alright with you. He said no, don't make up your mind. No, I would like number 3. This was effective population size in Drosophila, population cages. And I could see that this was a great topic for me, and somewhat reluctantly he let me get started right away and it was everything I wanted, but during that year I began to also become very much interested in human genetics. Fortunately Crow was quite a generalist. He had a student at that time in Neurospora and several in Drosophila, and so a human geneticist he could take in his stride. I actually worked my way through graduate school doing Drosophila and was happy to do that. Kind of interesting. And Neel was looking for someone who would be competent to analyse the data, but not sufficiently senior to take it out of his hands and so I was happy, he was happy and I had a marvellous time there. Also Jim Renwick, who you may remember?

PSH. I do indeed.

NM. He was in Japan at that time and we became very friendly. Neel had managed to get an agreement that when he was free, which was generally one day a week, he could be at the Atomic Bomb Casualty Commission, because Hiroshima was the British occupation zone, and we had a marvellous time.

PSH. Just before we spend a bit of time on the period in Japan, when you were with Jim Crow, am I right, this was before he had set up a human, medical genetics department?

NM. Yes. The department at Wisconsin, when I went back, in Japan there was the head of the group, Bill Maloney, he was a haematologist and he drew my attention to the elliptocytosis pedigree and to the linkage problem. I knew about that and I used the methods that were then available, which was Fisher's u scores, marvellous methods, but obviously very error prone at the levels of significance and with the kinds of materials that were then available, so I thought that would be an interesting PhD thesis.

PSH. Can I stop you just there before, because the sequence then. You went from Wisconsin where you hadn't actually completed your Masters but . . .

NM. No. I'd done it.

PSH. You'd done it.

NM. Because I had got started the first day I was there it was easy to do it in the year.

PSH. So you had a year in Wisconsin essentially and did your Masters with Jim Crow, and then went to Japan.

NM. With the understanding that I would be coming back, and at that point it wasn't definite that I would move definitively into human genetics but it was a possibility.

PSH. I have sort of got down what I think, I don't know, what might be your first paper as being with Neel, 1953, on the atomic bomb work.

NM. That was I suppose my first paper. There were some points of disagreement between the analysis done in Michigan and the one done in Japan. The head there was a man named Duncan McDonald, a very good person. In retrospect they really were small points, but when I got back to Wisconsin I received a telegram. Now in those days telegrams you usually got only when your parents had died. It was quite different. No one would phone. It would be quite out of the question. You will report at 1400 hours in Washington, and when I got there, there was a table, it looked to me about a mile long, with a bunch of Admirals and Generals in uniform. You see this was in '52 and they clearly understood that Neel had been a captain in the medical corps and that I hadn't been, so they were fairly sure who was right, and Curt Stern was there and I felt I was being put into a corner where I either had to fight or be a chicken. And so I was just about ready, knowing that I would be squashed like a fly, and Curt Stern told them a little story about the war in Germany and how, and this was the first world war, and how maggots would go into a piece of cheese from different directions, and by coming from different directions they could eat it all instead of just part of it. And he said, science is like that and disagreement is good, and both of these points of view are eminently defensible. And so that worked out well. And Neel and I had a kind of, we both liked each other I think, but we were always fighting. If he said black I would say white and vice versa. Then, quite late in life, we were in Brazil, which we both loved, at a meeting and we went off together to the botanical garden and then to the Stern emporium to get presents for our wives and for the next 10 years we were very friendly and really couldn't remember the things we disagreed on. Of course genetic loads were one thing because, coming back from Japan, Jim Crow had told me that Muller was going to be with his daughter Helen in Hawaii, and so, I knew Hawaii, well, met them and talked about it, and issues were then involved, which was the degree of heterozygote expression for recessive genes and that genetic load theory came really out of that experience and the stimulus of talking to Crow and Muller.

PSH. Did you have much contact with Bill Schull in relation to the atomic bomb work?

NM. Yes, I met him just before going to Japan. He loved Japan.

PSH. He has written that beautiful book.

NM. Yes, his Japanese was good and it was just, I enjoyed it but not as intensely as he did. He was doing the analysis in Michigan at that time and so we corresponded a lot. And in fact he had expressed an interest in the

consanguinity, more from a social standpoint than a biological one, and Jim Neel was sensitive to this issue. He said you can work on almost anything, but sort of avoid consanguinity. So I said, well I think my ideas are somewhat different from Jack's and no one could quarrel with Jack. He was, is a very likeable person, so there's no possibility of quarrelling as you might with Neel if you had to, so I said spell out all you want to do and I will avoid it completely, but I think that what I want to do is different. And he was busy so he didn't reply to that letter and then another letter. Didn't reply to that so I said to hell with it and so I made a report that did everything that I wanted to do and gave it the two names, me and Schull, and I think it caused a little bit of concern at the time but ended all very happily.

PSH. And you did publish on that?

NM. Yes all quite amicably.

PSH. Tell me a bit more about Jim Renwick, because I had no idea he was in Japan then.

NM. He was serving, because he had done his medical training during the war he had the obligation to spend two years in the medical corps and the British were represented really just by the medical corps there. The commanding officer was a major and Jim was interested in all aspects of classification of malformations and he was just developing his interest in linkage and we would talk about that a lot, because of the fact that there were dominant pedigrees to talk about.

PSH. It must have been before he went to the Galton.

NM. Yes, but he went to the Galton very much interested in linkage already, and immediately went in that direction, and Jim was a remarkably successful individual in an idiosyncratic way. The Americans were trying to learn elementary Japanese. He decided this was a waste of time and he would get on a train, go to a remote part of Japan, get out and say 'bring me someone who speaks English.' Everybody wanted to speak English. You could stand on the street in Japan one time a child apparently having heard about Walt Disney and he said "What's up Doc?". And then Jim disappeared from our group for several months and came back. I said where have you been and he said, it was in the Korean war, and after that happened well the major had seen a soldier with spots and said "Smallpox. Vaccinate the men". And Jim said "Nonsense. It's mosquitoes." According to Jim he was right. I think he was, and the next day he was in Korea.

PSH. When you got back then from Japan, did you return to essentially your previous post, or to a definitive post?

NM. Oh very much so. Jim Crow had a grant from the AEC to study mutation in Drosophila.

PSH. Sorry the AAC, that's the American Association against Cancer?

NM. No the Atomic Energy Commission.

PSH. Ah. AEC. Sorry.

NM. So that provided my enormous salary, I think it was about $2,000 a year and on that I could go to concerts, but my thesis was on lods. I had had the good fortune that Abraham Wald, who developed this, was a refugee from Germany and he did it as a secret wartime activity. The problem was that if you wanted to drop bombs on Germany, if you want all your bombs to explode, to test them you have no bombs. Conversely if you want the maximum of bombs, you fly over, you drop them, they are duds, you lose your plane, so obviously you wanted to verify that the bombs are effective, but still keep most of them to explode and it turns out that that kind of analysis that he developed was extremely good for that. It was obvious it would also work quite well for linkage, and so that was the origin of lod scores. And because it was a war time secret, he was not permitted to publish until '47 and it took the world of statistics by storm, so in my elementary statistics course I learnt all about sequential analysis models.

PSH. How come you made it a PhD project, because I mean, back at that time it must have seemed perhaps almost a bit of a shaky thing to found a complete PhD on?

NM. Well, there had been this succession. Bernstein, in about 1930, was the first person who recognised that you could detect linkage in principle in humans, even though it was non experimental, and then Haldane, Wiener and particularly Fisher developed very, increasingly elegant methods. In those days there were so few people working in the area, it would be a period of several years between one paper and the next. So every paper was better than the one before. That's not true anymore. It was clear, Sylvia Lawler and Harry Harris were finding isozymes, taking Oliver Smithies' approach and so in addition to the blood groups, you were getting a lot of markers, which seemed very exciting. The idea that you could now have possibly 20 million snips was alien to us at the time. So linkage data were coming and people were working extraordinarily hard to exploit it, and elliptocytosis and Jim Renwick and others, nail patella syndrome and other things, after of course the initial discovery in '54.

PSH. Can I ask, at Madison was there a blood group genetic marker lab already established by that stage?

NM. Oliver Smithies was there, so there was a lot of starch gel eletrophoresis and there was a good deal of blood grouping done in Irwin's lab with cattle, and we did a little bit of work with that, but the human genetics department wasn't founded until '58 I think, and the way it happened was, when I got a PhD using lods as my thesis, and there was no doubt that linkage was working, it just wasn't working in the way that it subsequently did and I suppose, you know, in a sense if there hadn't been human linkage, I suppose there might not have been Watson and Crick in a way. So I was offered a post in Wisconsin and, following the example of several American universities, there wasn't enough impetus to have a department, certainly not for a young PhD, and so the question was to go into the anatomy department, I knew nothing about anatomy really, and from that position they had many teaching

hours. Of course as a teaching programme it wasn't at all successful because the students would ask 'will we be examined on this' and the answer was no, and so that was the end of it. They didn't learn much genetics under those conditions.

PSH. That's not changed at all, has it.

NM. But particularly bad if you are from the vantage of the anatomy department. After two years of that, Josh Lederberg had just got the Nobel prize and was offered the post at Berkeley, which fortunately fell through, because his idea when he saw it, the new building, this was fine, but there is too much wall space wasted with windows. Now I want you to close up the windows and they decided he was a bit difficult and so that position didn't come through and the Dean of the Medical School in Wisconsin offered him a department. So the idea was to have Cavalli there who worked closely with Josh during that period and they tried to put down Jacob and Monod, Elie Wolman, with a circular chromosome I asked Wolman later how it happened that Josh, who had been so forward thinking with bacteria, couldn't accept, he said its just that he's learnt genetics. He's learnt that circular chromosomes were abnormal, so you couldn't have bacteria getting along only with circular chromosomes, and besides, the Comptes Rendus Academie Francaise, these came out as little squibs, very characteristic of that Journal, and you couldn't be quite sure whether you were repeating the same experiment, and he and Luca for months used to come in every morning, sure that today we'll show it's wrong. And at night they dragged their way home.

PSH. Just to go back to your thesis and the lods, can I ask, in your thesis was it purely on the theoretical basis or did you bring in some of the practical linkage work that you'd been involved in?

NM. I could see that it was going to be more than a thesis. That I would continue to be interested in that, so I graduated in '55 I guess.

PSH. That was the same year as you published the paper

NM. I published the paper, and there was no change. It was word for word the thesis.

PSH. I'm interested because I carried that paper around with me for ages and it is quite bulky and it almost looks like a thesis.

NM. Yes it was, and in '57 or '58 I met Penrose, who was a sort of God figure for me and I have always regretted that initial discussion, because I was anxious to ingratiate myself and he said "Do you really believe in this sequential analysis?" And like St Peter on a similar occasion at Gethsemane, I said "Oh no no no, of course not" and I felt like I didn't live up to that occasion, but anyhow in the end he published with Sheila Maynard Smith, I guess a somewhat enlarged version of the thesis and lods became accepted. Everyone except Norman Bailey. Someone asked him why in his book, which is about 1960, he didn't include lods and he said "Well in their paper they didn't include me". But by then lods had swept the board.

PSH. Before then you mentioned the blood disorders or characteristics, and am I right, it was then Moloney who was the haematologist?

NM. The first elliptocytosis pedigree of which I did a linkage analysis, was one from Japan. It wasn't very informative, but meanwhile Renwick and Lawler and Harris and I guess Bette Robson were showing elliptocytosis had strong evidence of linkage, but there were pedigrees that didn't seem to show it, and Penrose, interestingly enough, he liked chromosomes and it occurred to him that perhaps there may be inversions, polymorphisms like Drosophila, and he didn't think at that stage that, after all in Drosophila you have several genes for red eyes and brown eyes and white eyes, and the obvious suggestion was without chromosome rearrangement but with two or more loci, and the analysis was particularly clear because these were big dominant pedigrees from something that wasn't usually fatal. So at that time, I was able in those two years from '55 to '57 to analyse every piece of evidence on human linkage. Imagine that that was possible then, including Haldane's claims of partial sex linkage and showed that they were not right. It took off from there, largely I think because of the somatic cell hybrids and the development of Smithies' starch gel electrophoresis.

PSH. So the blood characteristics, one of the things you looked at was this Pelgar.

NM. Anomaly. Pelgar-Huet

PSH. I've never been quite sure what it is.

NM. It would be hard to say very much about it. The haematologists were quite sure they knew what it was.

PSH. So the haematologists then, they were in Wisconsin?

NM No no. These were in Japan, because of course with the atomic bomb, a big part of the immediate effects.

PSH. So you started that in Japan and carried it back with you so to speak to Wisconsin?

NM. Yes. It was a very agreeable time.

PSH. At that time were you in close touch with, I'm trying to think of the other mathematical and also blood group geneticists that were around. I mean was Sewall Wright still there?

NM. Sewall Wright retired from the University of Chicago at 65 and he went to Wisconsin about 1953 I think, somewhere in the 50s and lived and worked there for the next 30 some years of his life, and was of course tremendously stimulating. His interest in human genetics was not so strong. Malécot, whom I met through Crow, Crow was a great, well he liked both aspects of it, and in fact I met Sewall Wright when he was still in Chicago. Crow and I went up on the train and saw him, and it seemed to me that he was not really listening to the problem we had, which involved effective population sizes.

This was in the first days of Drosophila, and he was polite but seemed somewhat distant. And coming back on the train, being a very brash young man, I said "You know I think there's room at the top." Next morning we got an eleven page handwritten letter, answering all the questions that I thought he hadn't heard. All of them! So I realised you know, there may be room at the top, but it's not easy to occupy it.

PSH. Yes.

NM. But I was lucky too, that in 1961 when there was the second International Congress of Human Genetics, I missed the first one, I was too young.

PSH. This was Chicago one wasn't it?.

NM. No, no, this was before Chicago. The first was Copenhagen, the second was Rome and there was a group of three Israeli scientists, a Drosophila geneticist, a haematologist and a very charismatic chap who was a bit of everything, including a kind of amateur in population genetics. He had had the experience during the war, when he was serving with the British Navy at that stage, later served with the British Army, of being on a ship that docked at an Italian port and a British nurse went ashore and came back with a classical case of favism. So in presenting it, he had ascertained that she had come from Cornwall and it occurred to him that when the Phoenicians went to get tin in Cornwall they might have been momentarily swayed by other possibilities.

PSH. Yes. How long were you altogether in Madison?

NM. Altogether, well effectively I left in '62, so eleven years.

PSH. So in '62 you went to Hawaii?

NM. No, I went first to Brazil, because following this genetics congress in '61 I was, in those days the question was very much open. There were not many polymorphisms known of course, and there was still a tradition that said every polymorphism was maintained by selection, and it was believed by many people. Dobzhansky on one occasion said in his Ukrainian accent, White Russian accent "All genes are heteropic but some genes are more heteropic than others". And so this was being argued and there were a lot of polymorphisms and so, working in a population that was subject to, well in those days to fairly hard conditions, not as hard as some of the ones that have turned up since then, but pretty hard. And so during that time I was approached by Hawaii, I had spent a few months there doing a study of inter-racial crosses after I'd thought left Hawaii for good and the new medical school was being started, so I was offered the genetics department. Larry Snyder was there. He was leaving the presidency and was going back into academia at that point, but there was nothing much else. And one of the men from the zoology department contacted me while I was in Brazil and I was disappointed that, when the medical genetics department was begun under Lederberg and when Lederberg finally did go to Stanford Jim Crow became the head of the department, and this caused a lot of unhappiness in the older men.

Wisconsin was, to some extent is, probably less so now, fortunate in having in the end two Nobel Laureates in genetics and several Members of the National Academy. So the old men, led by Alexander Green, who was a very strong person, became concerned that the core of genetics had been divided. The same sort of argument that went on in Oxford and Cambridge I suppose, that it's a great problem that the medical school was going into genetics because genetics was in agriculture in Wisconsin and as a young man I would argue that no, the resources devoted to genetics had doubled. Nothing has been lost. It's gained. Didn't have any effect. Every week we met and talked about this and I could see that I would find myself disagreeing with the senior members of the department, probably for ever, and Crow was ambivalent about this. It could go either way.

In the end they prevailed, they expelled the agriculture people, pretty effectively eliminated the medical side of the department. It was a huge department. Not quite as big as the hospital here but pretty close to it. Very few people recognise the names there any more, except for some of the old ones. I think, I suppose in retrospect it was inevitable, but it nobbled medical genetics at a time when it was taking off. Smithies,
Cavalli and a couple of other people who were in the department had I felt considerable promise, only to be forced back into the older community minus its agricultural element which contributed a great deal to it.

PSH. So you got to Hawaii in, was it '62?

NM. '62 Yes.

PSH. And am I right then, this was a chair.

NM. Back after two periods, yes.

PSH. Yes, after Brazil. Was this a chair of genetics rather than human genetics?

NM. It was a chair of genetics, but it was in the newly formed Medical School, so I thought this was a good opportunity to combine them. But then I found that I wasn't very patient with the administrative responsibilities and it got more and more difficult, very difficult to recruit good staff, because there weren't many geneticists on the market and it turned out that in a small group, two of them were British, because effectively they were part of the small group that were available. I think insofar as America was responsible for brain drain in genetics, it was more because we couldn't think of any other way to recruit people. We weren't necessarily aiming for the best, and the best tended to stay of course. So I remember that I finally reached breaking point when somebody said "What are you going to do about the chicks". I said "What chicks". "The ones that were eggs in the incubator and they hatched. What are you going to do with the chicks". I said right, this is it. I'm in the wrong post. I am not an administrator. So I went off and had a laboratory of population genetics and I was very happy with that loose relationship.

PSH. So this really was outside the main structure of the genetics department.

NM. Yes the lab was, and it was one of eight or so, one of the smaller ones I suppose, separate things and the legislature was by-and-large not terribly sympathetic, because they couldn't quite see, that friction. The medical school has recently moved from its home on the main campus, which I thought was a big advantage to be on the main campus, into a site in the last just about a month, down on the ocean front which means they have no library, in the belief that they would get enormous sums of money and lead the economy. Sounds hopeless.

PSH. Did you find the fact that Hawaii is an awful long way away from anywhere. Was that a disadvantage scientifically or intellectually?

NM. It wasn't, so long as I was working on population structure, and in particular I liked working in Micronesia tremendously, because achromatopsia when I started working was just the Pingelap eye disease. There was even a suggestion that since it come to the attention right after the war, that it was somehow caused by deprivation in the war, same sort of argument that went on in the department when I worked in Guam, but in this case it was a simple recessive and the historical genetics was very straightforward as to how it had spread in the population.

PSH. I was going to ask how you came to be involved in the Pacific Island, Micronesia, work; was it simply because those small islands related to Hawaii?

NM. Well Hawaii goes through phases of contracting and wanting to train students to find jobs in Hawaii, which is difficult, and wanting to embrace the whole Pacific. They do have this contact with China, and Japan and the Philippines are still alive in people's imaginations, so working with people who were going to Guam and Micronesia and Carlton Gajdusek going to the far western Carolines it sounded interesting and somehow I read about the people Pingelap eye disease, could be genetic, might be environmental. From the studies we have done in Hawaii with inter-racial crosses, the notion of genetic epidemiology came up and I mistakenly advocated that order of words. Neel had suggested epidemiological genetics and you can see why I would do the opposite, but I think his was the better choice in retrospect. Probably didn't affect the outcome. But what I was interested in was population structure. There had been a typhoon in about 1775. Nearly everybody died of starvation after the typhoon, not during it, after it, and so the pedigree, as it turned out, was just the last opportunity to get complete pedigrees of it and the neighbouring island of Moke and it was very straightforward. I remember out of 5% of the Pingalapese and some other Mokalese had this condition that was easily recognised at birth by the family members. Diagnosis was not a problem and in one case only there was a question raised as to whether both parents carried the gene. You could see that they came back from the same common ancestor, but in this one instance it didn't look like it. I asked some people of that age group. The mother of the family must have been quite an attractive woman in her youth, so she might possibly have been involved in a little bit of shenanigans and so I asked "Do

you know this person? Do you remember her when she was young? Do you know about the family?" And so it immediately turned out that that child was from a different father. And that was out of about 100 or so affected pairs and that was the only one where any question was ever raised.

PSH. Do you know, has anybody ever been able to go back since and track the mutation through the population?

NM. Oh yes. Well, it was tracked effectively but has been positionally cloned now, and they all work fine.

PSH. Now one thing that is really pretty significant, part way through your time in Hawaii, was Pat arriving there, and I know that she and probably you have always felt it is important to keep your careers separate, but it must have had quite an influence really.

NM. Yes, of course it had. She was spending a year away from Edinburgh. She'd actually spent some time working with Drosophila in California and Seattle and during the course of this she had some data to analyse and so we met each other and knew each other. It was recognised it would be highly unsatisfactory if she was to come into my unit, which was something of an irregular group anyhow. Very good group of people, who did well from there but it would not have been good for a marriage. So the Dean of the Medical School was very anxious to offer her a post and she went into the Department of Anatomy, so we managed to maintain this, each with their own group. We did the same thing when we decided that Hawaii, as molecular biology developed, was too isolated. It hadn't been true so long as we were doing population studies, or in her case chromosomes in fetal deaths, but it was becoming a serious problem. So we looked for a place where we would be in different departments and we thought we had the ideal situation because I was at Sloane Kettering. She was in Manhattan and she was across the street in Cornell and Josh Lederberg was President of Rockefeller. I had rights to play on their tennis courts - perfect. The only thing we hadn't anticipated was that we weren't really New York people. At the end of the first year each one delicately came to saying, you know, this may be a big disappointment, but this is not where I want to spend my life. And so we agreed and it just so happened that there was recruitment informally to get a successor here and so it seemed to work out very well.

PSH. Staying with Hawaii for a minute, the work which you, and for that matter Pat did on different aspects of mental handicap, would I be right that each of your work must have had some impact on how the other worked and felt around it?

NM. Well certainly the analytical side that had surfaced in Edinburgh as well. So we tended to be involved in that. Of course it was a time when the molecular genetics was, certainly in Hawaii but probably more generally, was not so well developed. The incredibly high number of genes that cause mental retardation, deafness and blindness, or for that matter limb girdle muscular dystrophy, anything was an order of magnitude at least more than I estimated as being the minimal number. Well the minimal number was

certainly minimal, but I didn't anticipate just how far off it would be. I suppose even the medical genetics people didn't expect it to be quite that complex.

PSH. No. I was interested because you wrote a paper citing Penrose's Colchester study as I suppose a paradigm. Did you actually have continuing direct contact with Penrose, or was he just more or less an example?

NM. Actually I had some contact with him, but the last contact with him was very shortly before he died in the early 70s. I had a section on human population genetics at the International Congress in Paris and he was one of the speakers and Gustave Malécot, and Jim Crow was the third. At the beginning of it only Crow turned up and he said if you want me to, I will keep talking until they come up and Malécot did turn up almost immediately and then Penrose. Penrose had had a heart attack and I was terribly afraid that I was responsible for getting him to Paris and having died, but he gave an excellent talk, which was widely misunderstood, because he was speaking particularly about the British contribution to science and Jerome Lejeune just did everything possible to rip him to shreds, because he hadn't mentioned the French contribution, and he said that wasn't the subject of his lecture.

PSH. I remember also that actually Penrose called it the English contribution, so presumably people like Pat and the Scots would have also been upset.

NM Well, Pat was born in London. Haldane and Fisher, Fisher, one of his daughters was married to a statistician in Wisconsin, and so I saw a great deal of him and a fair bit of Haldane, and a lot of Malécot, so I'm not quite the last person to remember, Crow certainly and a few other people but there aren't many left who have that recollection of how different they were as people, each very unique personalities.

PSH. Yes, they must have been I suppose, perhaps especially for an American they must have been quite puzzling as characters, how they functioned.

NM. They were. In '61 I was just delighted to meet Haldane, because he was one of my Gods naturally, and he and Helen Spurway had this meeting that the Israelis had put together and the French, Sheba, almost their surgeon general during the early wars of Israel and so everywhere that he went people treated him extremely well and he kindly went around and made sure we enjoyed ourselves. I met Haldane and tried to ask him a few questions and he seemed to be completely switched off. He said "Oh I'm not what I used to be." He did experiment on himself a great deal and see what happened and then he blacked out with lack of oxygen, so I felt there was just no contact, And there was a dinner at Carmel and he and Helen Spurway, in Indian garb, stalked out because they felt that their hosts were surreptitiously feeding them pork and as good Hindus they couldn't take it. It was really bizarre.

PSH. Do you mean beef rather than pork?

NM. No I think - beef. When they had suspicions they nursed them as much as possible and then he was the honorary president and he gave the most fantastic presidential address. He quoted for I should think half an hour from

memory from the Old Testament, particularly about David and Goliath, because he said, he always thought of himself as David and you know how big he was. He was much more like Goliath really. And he said, more than anything else he would like to have some pebbles from the brook in the Gaza strip, Ascalom, whatever it was, where David had taken to shoot at Goliath and the Israeli Government presented him formally with these things and when he died he had taken to using them as worry beads and when they fell from his hand, Helen Spurway knew that he was dead.

PSH. That's interesting.

NM. And I asked one of the Israelis you know, did someone actually go into this hostile country and get killed? Did they really go and get those stones? They said well, they came from that brook, or one very much like it. A few years later at the Genetics Congress in the Hague he did the same thing again, even better. In the first thirty seconds he'd hit the Pope and the Queen of the Netherlands, then he got into genetics.

PSH. What year was it you moved over to Britain?

NM. It was the first of January '88.

PSH. That must have been quite difficult. It is always more difficult finding careers for two people than one, and posts that are suitable. I know from Pat, and I remember how it happened, about her post and how that happened, but how did it happen that the MRC and others produced something for you?

NM. Well it was the CRC, the Cancer Research Campaign, who largely supported us. Well, it was a strange position because Southampton at that time, it was understood that some universities, Cardiff was one and Oxford and Cambridge, had successfully and profitably established a genetics department, but with David Barker here there was no enthusiasm for genetics. Possibly it was a good idea for the future but its time had not yet come, but they had a Department of Community Medicine which was somewhat shrinking, a delightful head who took early retirement, but they had some space, so this was on offer, but before we got to that point I remember phoning the Dean of the Medical School, in the days when Deans really acted like Deans, you know sort of a one man show.

PSH. Their word was law.

NM. Well no, but really very gentle and not the complexity of modern administration, but explaining that I was interested in doing this and the reason for the interest was that my wife had been offered a position, and if she were to come here I would be interested, and that you might have noticed that I'm American. I got "I surmised as much" or something to that effect. And anyhow it worked out really quite well, although Southampton was still among the last to establish a genetics department, just before Bristol. No Bristol hasn't done it yet.

PSH. No it hasn't .

NM. But it's still playing funny games with social medicine, but that worked out quite well, then when the head of community medicine took early retirement nobody bothered me and I wasn't one to bother with them. I moved over to clinical genetics in the next building; that was very good. I liked that a lot. Then when the department was founded I came over here. But I think perhaps in retrospect the university really had a rather short period when it was interested in genetics and now some other catchword has caught their attention with the possibility of getting a new building has come out, so I don't think they had the consistency that would be required to establish a strong department.

PSH. Having worked for most of your life in the American system, did you find it strange or frustrating, the kind of way the British system works or sometimes doesn't work?

NM. Not really. It's a strange thing. I'm far too old to make a complete conversion either in speech or in thinking. What I find is that my understanding of America, my sympathy for the American president and things like that, have gone to quite low. I'm a bit in the Sargasso Sea of not knowing where I stand in that respect, but in some ways it turned out to be amazingly simple. A few years ago one of my colleagues here working with asthma, put me up for an honorary membership of the Royal College of Physicians, and as part of that occasion there was a routine letter "do you have any relatives who are members of the Royal Society?" and I remembered something that my mother had given to me and it turned out, fortuitously, I forgot that, but I found the copy. There was a chap named Samuel Garth who was physician to George IV and then Queen Anne and was knighted somewhere around that period 17, 18 - whatever it was. And the reason I knew about this was that the last of my family to move to America, must have been about 1820, somewhere around there, and in the family, because Garth had been knighted, they took pride, he was the only one in the family who was knighted. The family name was Friar so there was a succession of boys. This was customary in those days, Samuel Garth Friar and that lasted until about 1900. It's gone now. Don't know any Friars. And so the recollection of that stayed on and I was pleased that the Royal College of Physicians had moved from its old place which was panelled walls and kept one of the rooms and since he was a founding Member there was a painting of him across the room from Henry VIII. I felt it was not altogether unfamiliar in a way. Of course there are small differences the way things are done or might not be done. At the moment there is some tendency for people in genetic epidemiology to emigrate. Several have been lost in the last few years, out of quite a small group, but I think it probably reflects the inordinate support for a small number of very large programmes, so that the young find it advantageous to go elsewhere.

PSH. The number of people in what you can call genetic epidemiology has always been small, particularly more in Europe I think, and particularly fewer in Europe than in America.

NM. The Society I guess has 350 or so people and of these 20 were British, and of those, four have left and about the same number in France and Germany, so it's a heavily American group, that's true.

PSH. Do you see, looking ahead, any possibility for genetic epidemiology and conventional epidemiology really coming together, or do you feel that it might just have been better to call it epidemiological genetics and accept they are always going to be different?

NM. I think it would have been better, but I don't think it would have profoundly influenced the way things are going. But looking back on it I think Jim Neel was quite correct, that the epidemiologists are so numerous and they have at the moment so little understanding of genetics, that it is really very dangerous. The Human Genome Project was a great success largely because, although John Sulston was not interested in human genetics in any way, he was a very sensible person and he didn't try to make it a complex study. His position, as far as I can determine, was that they were there to get best possible human sequence, with the limitation they couldn't represent polymorphism, but that was their task. They weren't to tell people how to use it; the HAPMAP project is a little bit less clear cut because, despite the tutelage at the Sanger Centre, there is a tendency to want to tell people how to use whatever the product may be, and that is very unwise, because you can't foresee the use of . . . I think technologically it is an absolutely marvellous development, but they should restrict their activities to finding more snips. They are not competent in genetic epidemiology and they will I think regret having done this, and as for Biobank that is really I think pathetic. On the other hand Francis Collins is said to want to have one in America. I can't really see that it makes any sense. And the supporters for it are an unholy mixture of statisticians and epidemiologists and they don't seem to understand the problems, and Colin Blakemore I think has not thought this through. It isn't going to bring a whole lot of new people enthusiastically into clinical research. Quite the contrary. If they discover that clinical research means shuffling papers collected by nurses, they will avoid it like the plague. It's going to be counter-productive.

PSH. How do you see things developing in terms of common disorders and genetics, because I know from your writings, and I have felt very similarly, there is this contrast between how extraordinarily powerful linkage and related approaches have been in solving single gene problems, and yet I've felt there has been this naivety, that people had almost expected they could just do the same for another year or two and it would solve common disease genetics, and yet it hasn't?

NM. No, but it does take really an amazingly long time to see the significance. For example I can remember when Penrose once wrote he could see no possible application of linkage, it was just a sport, an intellectual puzzle. Sort of representing an old Oxonian tradition of doing nothing that had any practical consequence, and Drosophila wasn't that much different. Most people thought the chromosome theory was well worth testing, but the far reaching implications I think, this century in genetics would be unrecognisable if hadn't been for these four people, five people, working in Columbia. I think in the long term, the understanding of gene action has to come through this. After all with only 25,000 genes, each gene must be doing about fifty things, quite unrelated and unpredictable things, and this seems like the only way at present of answering those questions. It could be that other techniques that

are beginning to be practiced will change that, but then you have to be able to measure the gene effect and handle all the other problems associated with that, so I think that in modern terms the cost of $100,000 is not very much. I think it will be seen as quite a successful study in a way that I can't imagine that Biobank would.

PSH. I would agree with you, although hopefully enough people are doing their best to rescue Biobank.

NM. But it has gone so far now, that no one is going to rescue it by discontinuing it, and there is no indication that the people who are making the decisions have any genetic understanding. That goes for the statisticians you know, who are quite good at devising certain things, but they don't seem to have any feeling for the quality of the data and the kinds of questions that can be answered.

PSH. Just coming back a moment to Jim Neel, one thing which I know you were very much involved with and felt very strongly about, was rescuing his reputation from that extraordinary attack.

NM. By Tierney, yes.

PSH. And it's something that worries me very much that there have been a series of these character assassinations, which inevitably are damaging and I find it very worrying that this kind of thing can happen.

NM. Well, it's the sort of thing that I think has been encouraged by the attitude that some people represent the truth. The truth might be Marxist, or whatever their truth happens to be, and that in the pursuit of that anything is legitimate. Now in this case it just happened to come in that split between biological anthropology and social anthropology, and those two groups hate each other, so the opportunity to attack somebody who actually went out and drew blood you know, and tried to stop a measles epidemic and didn't succeed, oh boy this was just the sort of thing that would bring them out, and the chap who wrote it was a failed graduate student in anthropology. I think his career is an extremely interesting one because he originally wrote this book attributing the ruin of the Yanomamas to gold miners and he went and talked to a couple of established anthropologists, social anthropologists, and was told no no no, it was really the scientists there . And of course scientists buy books and gold miners don't. So from every point of view if you are going to pick on somebody in the Amazon, pick scientists. And it was a real smear campaign. It was all done in terms of a conspiracy that came out of the mad scientists, the Dr Strangeloves who worked with the Atomic Bomb Casualty Commission. It was a very bad effort and I don't know how many people have developed reservations about that. Where there's smoke there's fire, that kind of thing. There wasn't really a single word in it that had any truth at all.

PSH. No. Newton, just to finish, I have been asking everybody I've seen two things and one of them is, is there one particular piece of work which, if you had to just choose one, you feel you'd identify with that more than with anything else?

NM. Well, I mean, I suppose that it would tend to be the development of lods and the way in which it took over linkage, and of course much of my career has been working with problems which are no longer current, they are studies of populations and families. People don't go around estimating mutation rates and doing the things that were then consequential. The necessity for genetic load theory has passed in a completely reductionist world. Having said that, I take as much pleasure now in a more difficult situation. At that time there was no group or even consequential person fighting lods. It was pretty obvious that this was the way to go, and it worked and it didn't make the same mistakes and I am pleased that the false discovery rate, which was something I introduced then, solely to control the type 1 error that was excessive in those days. If you start judging linkage at the 5 percent level, then very, very little of it is true and it was a very satisfying time. But at the same time I have the same enthusiasm under the more difficult circumstances, because now I am not fighting at a personal level with anyone, but there are programmes like HAPMAP have managed to choose a somewhat dangerous path I think, in terms of what they hope to do with this marvellous source of information and what they want other people to try to do with it, and so I look forward with just as much pleasure next week, to seeing if it's possible to straighten them out.

PSH. The other thing I have been asking everyone is, is there one particular person over your career that you feel has been a particular influence, either in the early stages or at other times, or is it more a combination of people?

NM. Well I think it's, there's certainly a group of people, I mean obviously most people I think, if they are happy with their supervisor, will say that he had a big influence, I think he was very stimulating, but what I liked best about him was that, if I came up with anything I wanted to follow he would encourage me. I think that was particularly good, but also the fact that he was an excellent population geneticist.

PSH. That's Jim Crow of course?

NM. Yes. So many of those interests, I don't know that I acquired them there, but I certainly refined them . He was the one who introduced me to Neel and Schull and really made that possible. I suppose that would be perhaps the single most influential person; on the other hand Malécot, Fisher, Sewall Wright, Haldane and many of the people I worked with, some of them took degrees with me and generally done well. I think I have been very fortunate in the people I have worked with. The group here is just a delight. They are quite patient with me most of the time

PSH. Is there anything else before I turn the machine off that you feel I should have mentioned and haven't brought up?

NM. I was trying to think back over it. I think the profound change in genetics, which has certainly been characteristic of this century and hasn't begun to be fully expressed. There's a marvellous side to it, also I think a fair bit of risk. I have become quite interested in the last year in what it is that brings any human system from success to failure. I have been reading Alexis de Toqueville's big thick book about America and how he admires democracy but is concerned about its weaknesses. I haven't really found a good resource

to explain why Greece and China went downhill, after leading the world at a certain stage, because it rather looks as though science is at risk of following the same course. This growth of enormous enterprises is out of control and of course it has become so diverse that you can never hope to have a committee that understands very much about what they are deciding. But I've wandered away from the question.

PSH. No no.

NM. The question about who. At each stage there has been someone or several people who had considerable influence in one way or another. I think someone who was often at the time was an irritant but a Drosophila geneticist, Larry Sandler, who was a graduate with Crow a year or two after I was, and he was really obsessive about how in his view, human genetics was so much inferior to Drosophila genetics. And I found that very stimulating because you had to think about it. It's not a form of thought that I would have pursued on my own and I think he didn't actually see what was happening. All during the history of the Genetics Society of America I have heard good people saying, human genetics just doesn't have enough force behind it to exist by itself and it will come crawling back to us, begging for some fruit flies. I'm sure that for better or worse. Neel was a very stimulating individual on occasions. In the end we agreed on everything pretty much, so I don't think I could choose between the people with whom I had very amicable relationships and the ones who were somewhat testy or competitive.

PSH. I see in my jottings I've got two things down. One, how did you come to do the Barra study?

NM. Well, Pat had been going to Barra. She likes the treeless expanse, the ocean, the
colours and so on, and when we were first married we weren't sure how anybody reacts to Barra. It's not that different from the coast of Maine really, except there are no trees, and I very much liked it and there was a GP on Barra. At that time there was only one. We were very close friends. He was the one who actually came up with her cottage there some years later, but he took an MD in Edinburgh with the research he was doing on aspects of clinical genetics there, and I was very much interested at the time in the observation that, despite the close ties with South Uist, in part because of their Catholicism, but nevertheless there was very little inbreeding. There was Ellis van Creveld, very little for a population of that size, and of course it's because the sea is a highway, it's not a barrier, people were coming in from all over, certainly from Ireland but not infrequently from Poland and other exotic places. So it just happened. Everything all at once. Pat during much of her life has been concerned with population cytogenetics too, so it was all very, very congenial. I remember actually when we were collecting material one of the local people was up a ladder and he said "You don't want my blood. I'm from Aberdeen". She said "Aberdeen. It's what we want".

PSH. The other thing which I jotted down, your Allan award, it intrigues me. I am right you were the first person to have the Allan award?

NM. Yes. You see at that time there was no custom associated with it at all.

PSH. That's what I was thinking because you must have been very young.

NM. I didn't give a lecture. I was a year in Brazil and I thought this is very nice, but I am busy doing field work and in retrospect it was very thoughtless and almost immediately the custom of an annual lecture, but it just didn't occur to me as an urgent matter.

PSH. Mostly it's been given to very established people quite well on in their careers, so who would have suggested that it might go to yourself? Do you have any idea?

NM. I don't know at all who was active at that time, probably at that stage of our relationship it wasn't Jim Neel, but I imagine that it was because – I'm just speculating, that Larry Snyder and Charlie Cotterman had been active in the thirties and Charlie was all his life and he went to Wisconsin. But still it was an older kind of analysis. I sometimes thought in segregation in linkage analysis, that it was imaginable that some of these formulae existed somewhere in the notebooks of Haldane or Fisher and it just seemed impractical to apply them, and when the IBM 2000 came out, when I started to do this work with sequential analysis, we were wiring boards and there were punch cards and there was all this old machinery, would jam every so often and sparks would fly, and then the first IBM 360. It had 2000 small words of memory, incredibly slow, incredibly unreliable, but that's how those lod scores were first generated and it clearly meant that new techniques were being developed, that were being applied as part of the complexity of genetics after the war. After all human genetics almost seemed to have come to an end. Eugenics had discredited itself and there was certainly active discouragement if somebody wanted to take a PhD in human genetics in most places. I suppose there was the feeling that there probably wasn't much in the way of employment. This was that upward wave, as things in every aspect, in what was then called biochemical genetics and certainly in clinical genetics, and that must have been a choice among the people, probably some idea of picking a post-war entry into the field. Snyder and Madge Macklin, Nash Herndon were elderly at that point. It seems to have been something of a fluke.

PSH. Newton, thank you very much. I am going to turn the machine off now.

End of tape.