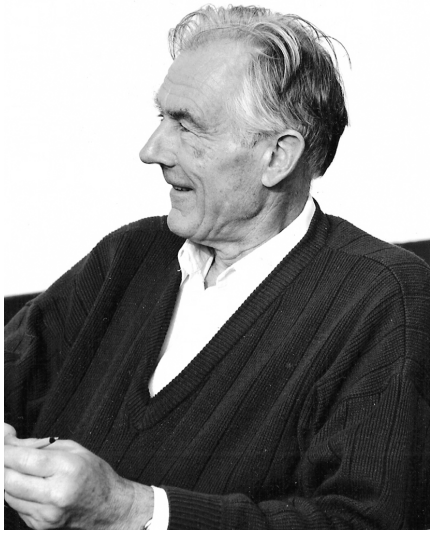
John Edwards



Personal Details	
Name	John Edwards
Dates	1928 – 2007
Place of Birth	London
Main work places	Birmingham, Oxford
Principal field of work	Theoretical genetics, Clinical genetics, gene mapping
Short biography	See below

Interview	
Recorded interview made	Yes
Interviewer	Peter Harper
Date of Interview	23/08/2004
Edited transcript available	See below

Personal Scientific Records	
Significant Record set exists	Yes
Records catalogued	Yes (in progress)
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Biography

John Hilton Edwards (1928 – 2007)

John Edwards was born in London and trained in Medicine at Cambridge University and Middlesex Hospital, London. After a year as a ship's doctor in the Antarctic and a series of medical training posts, he joined geneticist Lancelot Hogben at Birmingham University as lecturer, eventually becoming Professor of Human Genetics there and in 1960 discovering the first autosomal trisomy (trisomy 18) after Down's syndrome. In 1979 he was appointed to the Chair of Genetics at Oxford, remaining in this post until his retirement.

His wide ranging contributions to human genetics included the analysis of human genetic linkage, comparative gene mapping and the identification of X-linked hydrocephalus.

INTERVIEW WITH PROFESSOR JOHN EDWARDS 4 May 2004
(recording failed)

I interviewed John at his home in Oxford; 78 Old Road, Headington, close to Churchill Hospital and a fine and comfortable old house with a very large wooded garden at the rear.

John had written an account of his early years which he gave me – he had just done this the previous evening, having never written about himself before. The interview thus began more or less where this left off.

In response to being asked what influenced him towards science, he is clear that it was an early love of natural history, especially seashore and marine animals that he found as a childhood by the sea in North Devon, where his mother was convalescing from tuberculosis. This interest is also recorded in the notes he made. It is also clear that his rather solitary upbringing made unusual and reflective reading possible, even though he was slow in learning to read.

We spoke little about school years but he went to Cambridge where he read a range of subjects and was strongly influenced by lectures in biology [both vertebrate and invertebrate zoology which he took as additional subjects. It seems that his tutor [a classicist] was initially under the impression that he was to read Classics and offered him tutorials in classics: on being told he was not reading classics he countered by 'in that case I won't charge' and took him through books 1 and 2 of the Odyssey Not surprisingly, with these wide interests, he did not get a good [only a third] degree.

John states that at this point he did not have any very clear ideas on his eventual career, but he did develop strong interests at that time, particularly flying and gliding, but also a love of mountains and polar regions; he went to lectures at the Cambridge Scott Polar Research Institute and had read the books on polar exploration as a boy. He spent one long vacation in Labrador lumberjacking for the Grnfell Mission, later working in the Iron Ore mines in Newfoundland while awaiting a ship back.

His clinical training (Middlesex Hospital) does not seem to have been very *interesting at the Middlesex* – stimulating. He had his offer to assist at autopsies at the zoo in the mornings accepted, and later spent most of his time at the official 'Annex' the Central Middlesex Hospital. He failed to obtain a house jobs and while wondering what to do was offered a position as a ship's surgeon on an Antarctic Survey ship: they had no funds for a zoologist but were obliged to have a doctor. He was appointed after being accidentally interviewed at the Colonial Office for the Burmese Police. On return he became House Physician in Neurology at the Middlesex Hospital, before noticing an obvious tubercular lesion while being examined for conscription [he was found to have tuberculosis] resulting in six months hospitalisation [then the standard treatment for tuberculosis] after which he was advised to follow [a career] a few months in a 'banker's hours' job, spending six months in institutional psychiatry [at Knowle County Asylum] followed by six months in

pathologyat the Central Middlesex And then a very demanding house job in general medicine at the Central Middlesex. Around this time he developed a strong interest in biometry, and the problems created by the association of blood groups and disease in duodenal ulcers and gastric cancer. [Sir Richard Doll was then a registrar and had published on this]. It was here that he did his family study of Peutz syndrome (polyposis with oral pigmentation), involving considerable family tracing, and published in 1956.

His next post was at Knowle psychiatric Hospital [asylum]. He gained insight from seeing patients with schizophrenia and other severe disorders and was also impressed by the normality of the brain in the few autopsies he did. (one of his responsibilities). Perhaps as a result, he next took a pathology job at Central Middlesex Hospital.

We spent some time discussing the next phase of his career in Birmingham and Oxford. He was appointed in Birmingham in 1956 [to the MRC unit led by] MacKeown as a lecturer in epidemiology in a department loosely affiliated with Human Genetics under Lancelot Hogben, who interviewed him.

Lancelot Hogben was there as Professor of Human Genetics, still affected physically by some signs of mysoedema , after a thryroiectomy for thyrotoxicosis, but not hardly impaired mentally. John seems to have been given a free remit in his own work, but the epidemiology of anencephaly, with seasonal variation, was of particular interest and led to contacts with the paediatric department and with pathology at the Children's Hospital; these continued [through monthly visits] after his first move to Oxford where he was invited to join Jim Renwick in a new MRC department of Human population Genetics.

This move seems to have been somewhat of a disaster. Alan Stevenson had just moved from Belfast to direct this new MRC population genetics unit, and MacKeown had suggested John transferred [I was a founder member – moving to nothing] there to give more scope for genetic studies. Jim Renwick was also appointed but never actually took up post. It seems that promises were made that never materialised, so after two years [he resigned], followed by a year's lucrative and informative exile at the Philadelphia Children's Hospital; he then moved back to Birmingham.

The Oxford period was of great importance, however, in allowing him to develop links with the Harwell unit, where Charles Ford had developed expert mammalian cytogenetics and cell culture. John linked especially closely with David Harnden, who was there at this time (1958-1960), before returning to Edinburgh. It is clear that John's giving splitting material to the Harwell group was regarded as disloyal and deeply resented by the Director. All the Oxford samples died.

The discovery of trisomy 18 in 1960 was a key event. The child was a Birmingham patient, whose case was presented at one of the regular Birmingham Children's Hospital meetings he continued to attend. John describes his reason for suspecting a chromosome abnormality to be the presence of apparently unconnected abnormalities of multiple systems, unlike most Mendelian conditions but comparable to Down's syndrome.

The child died shortly after this and John took tissue samples, dividing them equally between Oxford and Harwell. The Harwell samples, mainly cultured lung, gave excellent results showing a small extra chromosome, thought initially by Charles Ford to be chromosome 17, but later recognised as 18.

It is relevant that the patient was selected for chromosome studies specifically because this was considered clinically likely, not as part of a larger series. (David Harnden, in my interview with him, stressed the value that John's clinical intuition gave in this and other later cases). The pathology was also expertly documented by Hugh Cameron, and the report appeared in Lancet a year later (alongside the report of Patau, Therman et al on trisomy 13).

We next discussed the important family report on X-linked hydrocephalus (with distinctive thumb abnormalities), *again found in a Birmingham patient*, following a letter about two backwards brothers near Worcester with an extensive and scattered family and published in 1961. Again this seems to have been a combination of thorough clinical work with genetic analysis.

At several points during the interview John stressed the importance of ensuring that research was done by people with real expertise in the field – that clinical work should be done by experienced clinicians while statistical analysis should equally involve people with *real* mathematical ability [to keep things simple]. Both he and Jim Renwick felt strongly about this and had hoped that the Stevenson Unit would develop in this way, feeling let down that it did not [especially after Jim Renwick decided to go to Glasgow to work on parasexual approach with Pontecorvo]..

In 1960, John wrote his paper 'The Simulation of Mendelism', strongly influenced by his biometric reading and contacts, but also (I did not ask this directly) by his epidemiological experience in Birmingham. He stated that he considered this the most useful paper he had ever written and seemed surprised that I had read it. He was also not aware that it was included in the collection of 'clinical papers' by Chakraborty and Schull. He gives the influence of Penrose and Cedric Smith at the Galton Laboratory as key factor; also the earlier papers of Haldane. He states that on this paper neither Penrose nor Haldane had any particular reaction to this paper, which to me seems surprising. [*They never mentioned it but I doubt that they ever saw it. Penrose, unknown to me, had expressed the same argument pointing out that what he called K – and Risch and Lander and others called, and still called lambda, and regard as a good guide to selecting suitable conditions, was formally irrelevant to the problem].*

John had several Haldane anecdotes – mainly about Haldane's exhibitionist behaviour at Galton laboratory lectures. He is disappointed that neither Penrose nor Haldane seem to have proposed Cedric Smith for fellowship of the Royal Society – something that never happened: he died without this recognition in his 82nd (check) year with two papers in press. [My proposal – Jim Renwick's dying wish, is confidential. He failed for the seven successive years permitted – dying just before I would have to break the news for the last time].

Returning to John's Birmingham work, we talked about the influence of Sarah Bundey, who moved there from Great Ormond Street Hospital with her husband. John clearly greatly valued her clear mind and skills of organisation; she seems to have complemented his own qualities. We did not discuss his HLA work, which was a major project while in Birmingham.

John's Birmingham Chair was not the continuation of Hogben's, which had been discontinued, but was ad personem. He expresses his disappointment that the planned redevelopment that was meant to bring together the children's hospital and the new maternity hospital, with genetics linked to both, [in a building designed for the purpose] never materialised.

After 20 years in Birmingham, John was invited to take the Chair of Genetics in Oxford. This gave more opportunities for links with Harwell, especially in relation to comparative gene mapping of mouse and human, involving Mary Lyon, and Tony Searle . This resulted in the 'Oxford Grid' (apparently so named by Victor McKusick). John was clearly a major influence in forming and maintaining the close links between mouse and human gene mappers, even though the computing approaches [he developed using AceDB, the worm software] had to be abandoned under 'bio statistical pressure', and he had to spend much of last year rewriting it in using the less powerful approached [used later were not ones he agreed with]. [There was nothing to disagree with – we had the monopoly, but the biostatisticians – the new priesthood – could not accept a program written by a biologist and a cosmologist in C- not even C++, could be worth taking seriously].

We spoke about Dick Lindenbaum, greatly talented, but seemingly completely disorganised, yet immensely devoted to his patients. A striking example, quite unknown to me, was his continued contact with the girl having Duchenne muscular dystrophy and an X-chromosome translocation [a key case he published and pointed out its use in localising the gene] to whom he used to send experimental gels to tell her how the research was progressing, [a how big a contribution she was making] *even when* she knew she was dying. Apparently he used to sleep on the floor for five years in the department at night, with food in the fridges and Bunsen-burner meals after his marriage broke up, causing some administrative problems after the Census found an unnamed person – identity confidential – on what was the Queen's property. He was allowed to continue when I insisted on employing a night watchman to protect our records should he be 'unwilling' to provide this service].

We also spoke further about Jim Renwick, who became a close friend. Jim, together with John's brother Anthony Edwards, founded the European Society for Human Genetics. John is definite that Jim Renwick's talent in genetic linkage analysis would have become the pattern for genome analysis generally, had it not been for the major dispute with Victor McKusick over the genotyping analyses. *John attempted to heal this, but in vain.*[Not so I am afraid – the dye was cast – Victor never goes back on a decision. I declined an offer to replace him with good facilities at Baltimore].

Finally I asked John, as in other interviews, which piece of work he felt most proud of. He was unhesitating in choosing his X-linked hydrocephalus study

as a piece of clinical work, with his paper ‘the Simulation of Mendelism’, as a theoretical analysis.

I likewise asked who had been the greatest influence on his work; he felt that many people had influenced him, but that there was no doubt that Penrose had been the greatest influence, even though he had himself never worked directly under Penrose or ‘at the Galton’.

After the interview we discussed a number of more general issues, noted in his own summary and including how best to make key early work available on the web, what to do with his own records and material and other topics involving the history of genetics. He has kindly given a series of important books, including successive editions of McKusick’s ‘Mendelian Inheritance in Man’ [mainly gifts from the Author and signed], Cedric Smith’s ‘Biomathematics’ and Race and Sanger’s ‘Blood Groups in Man’ to be part of the Human Genetics Historical Library.

Peter Harper
5 May 2005.

INTERVIEW WITH PROFESSOR JOHN EDWARDS, 23rd AUGUST 2004

PSH. I am talking with Professor John Edwards at his home in Oxford and it is 23 August 2004. John, you have already given me some very helpful notes about your early life. What I would like to do is to start off with when you went to work in Birmingham, first and may I ask when was that roughly?

JE. It must have been 1956 I think.

PSH. And am I right that it was really Lancelot Hogben that you went to work with?

JE. Yes, I actually hadn’t got a job. I had had tuberculosis and was quite wisely advised I think to do psychiatry because it was not very strenuous in terms of night work and so on, and also perhaps more important, as food was rationed, all the patients were busy looking after pigs and things and so food was a very high standard. So I think after that I saw an advertisement to work with Professor McKeown in Birmingham and that was the advertisement I actually applied for, without any very adequate credentials. To my surprise I was invited to come up and the only interview I had in any sort of sense was really by Lancelot Hogben, who of course was the great man who had done so many things and written so many books. My credentials were rather limited because apart from my technical address being Marylebone labour exchange, I was unemployed, I had just got Membership (1956) but I had only written two papers, one of them was actually re-analysing one of his papers with different results, so I didn’t feel I was in a particularly strong position.

PSH. Which paper was that, John, of Hogben’s?

JE. That was on the ABO blood groups and so on, which Hogben interpreted as being very, very highly mutable and I knew a bit that he wouldn’t know,

from working in the blood bank hospitals and things that in fact it wasn't mutable, so there must be another explanation. So that was a very strange interview and he was utterly charming, absolutely charming. It was in a strange place. It was actually in the laundry because he had got some features of myxoedema, having had a terrible time with his periodic hyperthyroidism and the treatment sent him a bit below par and you could see the radiation burns around the lower part of his neck and he had a retrosternal goitre eventually removed, major surgery. It took 5 hours with a very expert professor of surgery and so that had solved many of his problems, but he certainly maintained a myxoedematous voice and was extremely sensitive to cold, and so he had decided that rather than working in the medical school, which was the normal address for professors, he would work in the laundry and he found a basement room surrounded by hot pipes.

Anyway he was very charming greeting me, and started by saying "we nearly didn't short-list you. It was the reviews" and so I didn't quite know what to say. He said "yes they were very good reviews. We didn't think much of the referees or reviewers". One of whom was Jo Morris was very active, in whose department I was more or less squatting while working on various things, having no physical employment, and the other was Richard Doll who had been particularly kind to me and helpful. He was a Registrar with Avery Jones when I was a student.

PSH. Can I just ask then, I knew you had worked with Avery Jones but hadn't realised that Richard Doll was there. Did that influence you in your statistical and mathematical interests at that time?

JE. I think what interested me more was that I was only a student and one reason I didn't get one of the standard chairs which you have to get if you are going to do anything at all in medicine and a house job in one's own hospital was the fact that I was hardly ever there, because when I first went there I found it rather uninteresting. The only really high class lectures seemed to be given by the nurses, and the official lectures by the consultants, they tended to arrive late and unprepared and well-dressed and so on and it was really rather disappointing, so I spent the first, as I had done zoology in Cambridge, I invited myself to the zoo to do autopsies. I thought that might teach me something.

So I spent a lot of time at the zoo in the first 6 months or so of this rather strange course which they had, and then I discovered that the associated hospital, the Central Middlesex, had really very, very high standards and was extremely busy and so it was a better place to be. So I was just a student when I spent a lot of time in Avery Jones' clinics just because he was just so very, very good. They weren't anything very statistical, they were just extremely good experience. Because they had all sorts of people there at that time. They had not only Avery Jones, they had Gummer doing very high standard of surgery. They had Illtyd James doing neurosurgery. They had Porter as a neurologist and they had perhaps most distinguished of all was Walter Pagel, a Jewish émigré who was the consultant pathologist and had an extraordinary aptitude for diagnosing the dead almost without an autopsy. So it had an extraordinary high quality of work, including particularly acute medicine under Horace Joules, who was also medical director of the hospital

and was a very impressive and dynamic figure. Unfortunately he ended the last few years of his life with a high degree of mania, being incarcerated in the Maudsley. But until he went manic he did build up this hospital in an exemplary way with very high morale and high work ethic for everybody.

At that time it was all Health Service and entirely, there was no private practice and I think why they did so well was the Middlesex County Council, or whatever the organisation was, decided that these old workhouses, which they were originally, had to be upgraded best way of upgrading them, rather than have doctors present who did everything from obstetrics to surgery, they would have proper doctors, so to speak, who were especially trained in these fields and they just offered salaries of 50% above the going rate and . . .

PSH. That was far-sighted.

JE. And at any rate the West Middlesex Hospital and the Central Middlesex Hospital, if you were ill really was the better place to be than if you were well. In fact when I had tuberculosis I discharged myself or I never really got to the teaching hospital except I was diagnosed as being X-rayed for the Army, and I saw this X-ray, which is more than the Army did and I went and had a better one taken at the Middlesex and rather upset them I think because I said well, I didn't really want to be treated at the Middlesex because at that time they tried to have one patient with tuberculosis on every ward for the students and I discovered that the infection rate among nurses exceeded the cure rate among patients. At any rate nobody on the staff had any experience of this condition and I thought I would be better off under Horace Joules. Anyway that's another matter. That's why I was at the Central Middlesex.

PSH. While we are on the Central Middlesex, can I just check, am I right that you wrote your paper on Peutz syndrome while you were there?

JE. I think yes, I was, yes. I was there and there was a case which I came across, rounded off and took blood and so on, and got very excited. Working with Thomas Dormandy , who had been very thorough, and looked into it. I'm not sure which of us found this case but it was quite a large family and very co-operative and helpful, so after that I wrote to people about it and went around the country trying to find cases and collected quite a few. If I did write a paper it was a very short one and Dormandy must have done most of the work. I can't recall having written a paper actually, but if I had I'm certainly very much the second author.

PSH. I think you were the first author on it actually. I've got it in PUBMED but just let me look it up for a moment. You were second author, Dormandy TL, Edwards JH, 1956, Peutz syndrome, Gastroenterologia .

JE. Really.

PSH. It's wonderful these computer indexes. They now go back to 1950.

JE. I didn't know about that. I would like to think I have written on Peutz syndrome.

PSH. Well you have and I think the next one must have been with Felicity, because it is Edwards F C and Edwards J H on tea drinking and gastritis.

JE. Yes that was the only time I have ever done a tea test, which was appropriate I think. But it was very interesting because Felicity was doing all the work but all that happened was we offered everyone a cup of tea and it was very, very hot and waited until they started drinking it and we just stuck a thermometer into it. And there was no doubt there was quite a substantial difference in the mean temperature between sexes. I think women had it hotter, but people with gut problems actually were drinking boiling tea.

PSH. Good heavens.

JE. Which probably didn't help their stomach.

PSH. And may I ask was that where the two of you met then?

JE. No no no, we met, I hesitate to say but we had met at a lost property office. We had known each other as fellow students both at the Middlesex, but I think there was a stage where we actually met at the lost property office, being addicted to losing things.

PSH. Coming back to Birmingham then, it does strike me John that when you arrived in Birmingham, although you said you didn't really have any experience, you actually did have quite a lot of mathematical and statistical interest and that you had done some family studies and you were very well trained clinically. So you weren't entirely without experience were you?

JE. No, I can claim to have had some relevant experience and I was very interested in the genetic side. I had spent a year on a boat and took a library with me. Books were expensive and there wasn't a lot of room, so one of the books I did read actually was Finney's statistics. The reason I read it was because there were more pages per unit cost than any other book and so I did find it quite interesting and as a student I was very interested in gliding and that is full of extremely deep and confusing mathematical problems. For example, if you are going around in a circle, which you have to do to stay in an up-current, it goes up faster in the middle of course, so you want to get near the middle. But to get near the middle you have to go at a steeper banking angle which means you are sinking faster, so there is obviously a very interesting point where you don't want to get too close in. You are actually sinking so much you lose. So I was very interested in this and the interesting thing was that the mathematics just didn't work, because for reasons which I think are due to the fact there's turbulence and you are actually in some way like an albatross picking up energy from the turbulence. It seemed that doing what was wrong which was going fast and steep was often better than it should be. So I got very interested in certain mathematical problems which arose in that. But I can't claim to have had any great training in mathematics. I haven't been privileged to have any particularly distinguished teachers in it and I still haven't, I mean I find it very interesting and I have been privileged to consult people and so on, but my continental shelf is well inland at the back of [?], which seems to be the thing everyone has to understand.

PSH. And the year on a ship that you mentioned, that was your year as a ship's surgeon in the Antarctic am I right?

JE. Yes

PSH. Can I just ask, presumably being on ship like that gives you plenty of time to read, not much space to put things.

JE. That is true yes. There wasn't much to do. It was a very nice environment I am glad to say. A little dentistry and psychiatry, but I had almost no acute medicine and no awful problem of what to do, for example picking people out of very cold water and nobody had any idea what to do. I had read various things and they were all different. So there were quite a few problems which I had hoped not to have, which I never did have. In fact there was no very serious matter at all except in Port Stanley we had both diphtheria and scarlet fever. I thought these were rather serious matters but the Port Stanley diphtheria is apparently a rather mild well-known form which everybody has, is treated by blowing hard in your nose and the membrane detaches itself spontaneously.

PSH. Oh dear.

JE. I was a bit worried that it might not be so simple for the locals so to speak on the ship. And scarlet fever was also happening in the person who provided all the milk, which again is not an ideal situation, but they were both highly secretive, because if they got into the official reports it looked bad for the Chief Medical Officer, so these never I think saw the light of day and there was great opposition when I decided to send back home to get what was called a Dick test, because I thought I ought to find out about the people on the ship whether they, which you can only do with a Dick test and it seemed to be quite relevant. But anyway the idea of admitting to anybody in London that there might be such a thing as diphtheria happening in a colony which had such a wonderful health record, largely because it had only 2,000 people in it, there wasn't much scope statistically for being ill.

But I was very fortunate there was a very distinguished and very experienced Jewish physician who had had his various problems. He had survived the war, although being Jewish and married to an Englishwoman he'd carried on as a general practitioner in northern Germany, but when the Russians came that was too much and he had to go out with his children and his wife with no degree which was accepted in the UK, and eventually they took them on the Falkland Islands without an English degree and so on, and he was extremely experienced and I was very privileged to work with him on the few cases we had, including, the first introduction I had to Port Stanley was as the ship arrived there were two people at the edge peering with strange eyes, in that they had a strange glistening at the centre, and this was obviously a case of Marfan's syndrome, which even I could diagnose from 50 yards it was so severe. So that was very interesting; we looked at these cases. The other interesting thing was, this boy was ineducable and put at the back of the class and when the exams came out for the scholarship to England, he said could he have a set and they said "Oh well it will keep him quiet". So they gave him

a set. He had had no real formal education, he was just put at the back of the class. He should have been at the front so he could see the blackboard, but they put him at the back. And so he just pottered around doing his own thing, bringing books with him and anyway he got the scholarship for the year, and the headmaster of course was greatly commended for his superb tuition.

PSH. John we have strayed a bit from Birmingham, so can we go back there again, and we got to Hogben, but you really worked mostly with McKeown, am I right?

JE. It was quite a happy and confused situation, but yes I was working with McKeown. We were working on dislocation of the hip. He had a very able senior lecturer called Record and they were very interesting because they both had a rather different approach. At the tea breaks for example, they were both very enthusiastic gardeners but Record was an empirical and practical gardener and all his plants seemed to live. While McKeown was an intellectual gardener and the Monday coffee breaks seemed to consist of autopsies on plants with Latin names. So I was quite influenced in a way by this empiricism as opposed to intellectualism in biological activities. And of course Hogben was particularly strong on this. He expected that everybody who read Yeats would know what a strawberry tree was, and if they didn't know it and hadn't found out they weren't proper literary figures. Of course Hogben had a vast experience of animals and plants and he had a very direct approach. For example when he was working on haemocyanin and snails were a bit difficult to bleed and get enough blood, he spent a fortnight on a trawler which occasionally collected octopuses and came back with a gallon. So he really taught me the direct approach and the need that prior expectation based on some knowledge of the matter at hand was essential, and one could only really use mathematics in a problem which doesn't need very difficult mathematics, like medicine, if one could have some idea of what the problems were; got the right problem the solution wasn't all that difficult.

PSH. So am I right that the main area of your own work during that time was focused around epidemiology of neural tube defects?

JE. Yes, I got very interested in that because well, McKeown was very interested because, he was very far sighted. When Hogben went there he got the idea of record linking, using very simple methods of recognition and he was exploiting punch cards very early on and using the identity and the birth date and so on, he was getting
very good and clear linkages and he was building up this system which McKeown extended, the Malformation Register, and it was very weak on novel things, for example it missed people without any arms because there wasn't a tick list for not having arms, only for having odd arms and so thalidomide slipped through. And there was some extraordinary things which were missed out by the sort of punch card medicine and surveying, but the things which were regular and fairly common and well known to the health visitors, such as spina bifida, they worked very well and it was quite clear that there were enormous differences actually within Birmingham and so it seemed quite interesting to work on it and I was encouraged to do that by McKeown. I rather wished I had been a little more persistent actually. There was a very interesting epidemic of it in Aberdeen and I really wished I had shot up there

and interviewed all seven people who had had this, just to find out what they were drinking and doing and so on. Which was a thing I should have done and I am sure McKeown would have supported it, but it's too late now anyway.

I was also perhaps influenced by Penrose, who had written a paper which I could appreciate because I had seen quite a bit of these things, it was not quite in accord and it was clearly not a straightforward genetic difference. In fact McKeown made a very important observation on record; it had a seasonal effect but of course if the condition has a seasonal effect, the environmental influences must be very, very strong and so in principle it is preventable, although effective prevention now carrying on doesn't seem to fit in with any simple way with the cyclic effect. But nevertheless I think McKeown and Record's discovery of a cyclic trend in what was thought to be a sort of genetic disease or act of God or something which nothing could be done about, as soon as it showed a seasonal effect it seemed a very exciting thing to try and find . . .

At that time of course I was working on spina bifida and wanted to work on linkage and genetics, while my friend Jim Renwick was working on linkage and things, but ended up working on spina bifida.

PSH. Can I just ask, had you already made links with people like Jim Renwick and for that matter, Penrose, before?

JE. Yes, actually when I was working in haematology when I was working in general pathology for a year, for six months I'm sorry, as a junior person in the Central Middlesex and a paper came out by Penrose which I couldn't understand, so I consulted my boss, who was a very versatile intellect in haematology and he just rang up Penrose and so I went to see the great man and showed this to Penrose who said "Oh yes. That's wrong. I'll correct that". So he got down the book, corrected it and said "thank you very much. I overlooked that". So I was really a bit shattered by this and he was so charming.

PSH. Which book John was that that he'd written?

JE. It was an article in

PSH. Oh it was an article.

JE. I think it was something on the ABO blood groups, which I had been working on and I couldn't just make out just what he was doing and I thought it must be right, and anyway, so he was terribly helpful to me and said why don't you take in genetics, because there's going to be regional boards and there's future in it and so on and why don't you come and hear the next lecture, which is next week or something, when Jim Neel was giving his great lecture. So I came down to that, and that was when I was introduced to Jim Renwick to show me where the theatre was and to take me off and so on. So I had an interesting experience at that. And then I went over to the big meeting in 1958 in Montreal. That was a very privileged group, particularly as you

had to go by sea and I shared a cabin with Maynard Smith and Reeves and Renwick and that was quite an interesting little group, and we had our little table with Bette Robson and Sylvia Lawler, so I think I learnt more on the going and coming than actually in the meeting, but it was extremely interesting meeting to be at at that time.

PSH. That was the meeting where Lejeune actually announced or at least mentioned his results on Trisomy 21 is that right?

JE. Oh yes. Well he wasn't quite certain whether there was too many or too few but he knew there was an odd number. This was quite extraordinary. And then there was Chu. Ernie Chu had got wonderful results but he was just sort of moving into the field just because he thought it would help him in his botanical work. I don't think he really wanted to do more than just see if he could learn from mammalian cells, which he was extremely adept at doing, very brilliant techniques direct. For example he was growing cells very efficiently, which everybody else was having difficulty with infections and so on. He taught me a very clever trick. You rinse your hands in methylated spirits and set fire to them. And if you shake them quickly it is completely painless and whether it has an effect on bacteria I don't know. It certainly has a psychological effect on the person doing them, particularly on their visitors.

PSH. So is it fair to say John, that this time you were in Birmingham you kept up your wider links with people at the Galton and generally in genetics?

JE. Yes, I used to go to the Galton when I could and for meetings. Unfortunately I didn't get on too well with the genetic department there. It was highly mathematical and involved in the Didel cross and grandiose schemes with Mather and Jinks. Mather was very pleasant to me. It did seem a very strange situation that these highly mathematical things were being done which assumed a behaviour of living things, which was out of touch with anything I had ever seen on living things either human or in my interest in animals as I had done zoology at Cambridge, both vertebrate and invertebrate and took great interest in this. In fact that was one reason I was given a job on the ship, because they were legally obliged to get a doctor but they wanted a zoologist and so compromised by getting somebody grossly inexperienced but legally able to fill the bill. So I was very strongly supported in this by both McKeown and by Hogben, and in fact it was quite interesting because there was such a really big difference. There was a little canal going through the middle of the campus and it could have been the Pacific from the amount of communication there was between the genetics departments, Jinks and Mather, and the more direct approach of the human group.

PSH. Can I just ask John then, were Jinks and Mather in a completely separate university department to Hogben and group?

JE. Yes. Now Hogben, what had happened was Hogben had had his career slightly disrupted because he did actually have the position as Professor of Zoology in Birmingham, and then he was in Oslo giving a lecture just at the beginning of the war when the Germans arrived. And he had done an enormous amount to help Jewish scientists get out, not only get out but also get in and get jobs in England, and he was on the blacklist because he had

been very active politically in writing about apartheid for example. He was thrown out of South Africa for his views on apartheid, so he had very strong credentials for being on the top of the list of the Gestapo's 'most wanted'. And he was there with his daughter in Oslo and so to get back he had a terrible time and it took him about 2 years. He had had to get the train to Vladivostok. First of all he got across the border alright and stayed with his friend, a geneticist there [Dahlberg], who had written a book called "Race Reason and Rubbish" which Hogben translated into English. That was Hogben's title as he was addicted to alliteration, and then he got back on the Trans-Siberian Express where he had various problems, he with his daughter, all their money was stolen at the customs in Vladivostok or somewhere and everything which could go wrong did go wrong.

But he did actually get a few jobs while at Wisconsin and I think in Hawaii, and wrote a very important book on mathematical genetics, which I have unsuccessfully tried to get reprinted by Dover or anybody else. There is no copyright problem. Dover were quite happy about it, not Dover but the publishers were quite happy about relinquishing it. Why it was so important is because Hogben with his directness, he never liked using the differential calculus which makes things so easy of course in some applications, but he always liked to see things like Eddington, as billiard balls, and things he could see and visualise and so this book on genetics doesn't require a calculus because it is entirely what happens if you have got a lot of black and white balls and do this and do that and select, but you get into all sorts of mathematical difficulties, which he solved as far as he could go, which wasn't very far but of course computers only work in digits, so it's revolutionary because it can all be now computerised and checked and of course enormously extended.

But in fact the approach has never come about and the main developments in mathematical genetics now have assumed infinite populations breeding at random. It would be a little more realistic I think if they assumed a few hundred people who might conceivably meet each other and be of appropriate ages and sexes and produce variable numbers of children, which of course can be done by the finite difference calculus very easily, and of course if you change the conditions it gives widely different results, and this of course is a big problem now in genetics where things like the haplotype, Hapmap and all these grandiose schemes, sib pair analysis and so on, are all really based on non-counting methods or rather indirect methods. While the Hogben approach would be to treat everything in the first instance anyway, there is obviously scope for a very high grade mathematics in all fields, but in the first instance, otherwise it is like taking a microgramme balance to a supermarket. It just causes confusion. And there's rough data in human breeding, so variable and so rough, that it is very difficult to see how anything like the Hapmap project could have succeeded, whatever its credentials, when based on a hypothetical population of a peculiar nature.

PSH. John, from Birmingham you moved to Oxford for a spell; was that about 1958?

JE. Yes. McKeown had been very keen and I had spent a lot of time at the Children's Hospital. They were very easy going in Birmingham as long as you

did some work, they didn't seem to mind where you were, so I went on the ward rounds once a week and I went on a superb pathological study they had there. Quite illegal now. You cut bits off without permission and show the people and so on. But it was an extremely well run hospital with very high standards I thought they had at the Children's Hospital, so I was very privileged to potter around there. And I thought I would like to get into genetics. So then McKeown very kindly suggested would I be happier if I worked for Haldane or Penrose, I said "well actually I really would". And so he said there's an MRC Unit starting up and he would write to the new Director, so he did and I was invited over by Alan Stevenson who was the new Director, who was if I might say so, was a hypermanic and charming Ulsterman, and so I was flown off, met at the airport, taken out to meals and whirled round. He was so charming and very stimulating. So eventually, I was very impressed by his success in getting Jim Renwick as well. So I thought that would be wonderful. I felt I had a lot to learn from Jim Renwick. So this was all sort of fixed and everything and we made, quite independently actually, we made a few conditions of employment and both ended up with the same. Quite independent. One was that we would not have any statisticians around for the first few years and if we had one they had to be really top grade. And the other thing is we wouldn't have any clinicians or any doctors and genetic counsellors and all sorts of people who were then starting moving in; we would have nobody without membership. So we did make that in writing quite clearly and independently and to my surprise. I only discovered that later.

But then things started being a bit odd in the way it was, because we were going to be in the Department of Medicine with Pickering and that was a big attraction, but then there was a quarrel with Pickering and he was no longer and we of course were no longer persona grata, so we would then have to go off to the Churchill and that was a nice hospital. So I thought there's lots happening there, plastic surgery in particular and good paediatrics. That didn't seem to be a big problem. The next thing is that he had actually managed to create even bigger problems and there was no room at the Churchill. The Churchill is like a golf course and still is. There's plenty of room at the Churchill even now, in spite of massive building, so we had to be a special building outside the sort of dotted line around the hospital, had to be built just outside and while waiting we were going to be lodged in the servants quarters of the old mental hospital which was built in the 1820s or so, for the psychotic clergy with their personal servants. This went on at the Warneford Hospital but it was I thought a very good hospital, very talented psychiatrists and so on, so it was quite an interesting place to work, but I didn't actually move from Birmingham to Oxford in order to have no facilities and work in the servants quarters of a mental hospital, while a building was being built in order to accommodate us later. In a way we were not really persona grata with anybody or at least our boss wasn't.

Anyway the next thing I knew was that Jim Renwick discovered that Ponte had been growing these cells and, Pontecorvo in Glasgow, always had a brilliant approach to things. He had been working away, taking his own blood and making a clot of it and growing it up in horse serum and it was growing quite well. And he got some of these cells and he was very thrilled when he grew the cells, and the idea was they were going to wander about on a plate

where they would be quite nourished. They were wandering cells, the white cells, and they would fall down little holes and then they would get cleared in proliferation and he would do all the parasexual things he was doing, which was a wonderful idea. The only trouble was that after Jim Renwick had decided that this was where the future was and had taken his family off to Glasgow and resigned, and left Baltimore where he was again living in a very lively environment with Victor McKusick, it was discovered , I don't know if it had been published, but it was discovered that if you looked at these cells they had no centromeres, because they were horse cells, which was very interesting because if you grow human blood it is unlikely it will grow without all sorts of stimulation, but horse cells apparently at any rate when mixed with human blood seems to be stimulated into spontaneous growth. So anyway Jim was extremely happy there with Pontecorvo and worked away on developing linkage particularly with McKusick and his big families and things.

PSH. Can I ask, the time when you were in Oxford was that when you established links with people at Harwell?

JE. No, I hardly knew about Harwell the first two years. When I came back in '79 the big attractions at Oxford were the

PSH. I suppose I was thinking John about people like David Harnden there.

JE. Oh yes. I am so sorry. The Trisomy 18. This actually . . .

PSH. Maybe now is a good time to sort of concentrate on the Trisomy 18 because I mean you were involved and others at Birmingham, but David Harnden was

JE. Well he made it work. Yes, it was quite an interesting position, but every Thursday I used to go up to the, I'm sorry I think it was every, it wasn't every Thursday, maybe alternate Thursdays, I went to the ward round of the Children's Hospital. I kept up my contract there.

PSH. John, let's go back a fraction then. If we could start at the beginning of the Trisomy 18 story and perhaps start with the clinical side. How was it that you found, you discovered that patient?

JE. Well, I had been reading about these things and so on and I was interested, and particularly interested in the Datura plant, which has 12 chromosomes and 12 trisomic syndromes, all of which have their features that are disproportionate. Everything is disproportionate, but nothing is very critical, otherwise I suppose it wouldn't be alive. Anyway I had this regular visit to the hospital, where I had this very nice, I think it was a very good day, Thursdays, because they had the professorial ward round of the children in the morning and then in the afternoon or sometime there was the brilliant pathology, where all the bits and pieces which were informative, particularly the heart, had been prepared and discussed, and it was very highly informative and of course superb quality control of hospital standards. I mean, how a hospital can run without a casual autopsy approach I don't know.

PSH. Who was the pathologist involved?

JE. It was to start with, it was a very, forget his name, a German Jewish refugee who was, I will remember before you finish this. He had a very high reputation and he did everything including haematology, including all the rhesus blood grouping, which was mysterious. He was never known to make an error but when they looked at the reagents they had somehow gone brown with time and were quite a shock for the professionals who worked with blood group sera which didn't look like that and then, just as I got to Birmingham he retired and he was replaced by Hugh Cameron, from Newcastle and I think trained in London, but anyway he was an exceedingly able pathologist and ran a very high morale disciplined department. So he missed nothing and he had a very wide interest, particularly actually in battered babies, which he had a lot to teach us all about and, in a secondary category, I am quite well informed on battered babies because it was one of his, and sudden death in infancy, in which he was particularly interested.

PSH. And the professor in paediatrics in Birmingham then was?

JE. At that time, it was interesting, it was Smellie, who made his reputation as an adult physician and sort of drifted into it and he was succeeded by Hubble who had an interesting situation. He was simultaneously offered the chair of Medicine at the age of 50 I suppose. Simultaneously offered the chair of Medicine in Manchester and the chair of paediatrics in Birmingham, because he had just been doing both. So he was an extremely able physician of course and also quite a scholar, particularly in the eighteenth century medicine and literature.

PSH. So you came across this child, was this at one of the meetings that came up for discussion?

JE. Yes, I was very fortunate actually because I was quite interested in the Lunar Club and that sort of thing in Birmingham and the library had laid on an exhibition, so I changed my dates so that I could go and see the exhibition after the clinic. Very fortunately actually, and there was this case, which I was told "Oh an interesting case that we have got, I am sure you would like to see this case of Ullrich". Ullrich had all sorts of syndromes, none of which really existed, but he always put a hyphened name of somebody with some distinction. He had chosen this thing from some innocent and able woman who was an expert on mouse genetics in Oslo, or Bergen possibly, and who described some sort of syndrome and so he had got around to this and thought this was the same syndrome because he had a short neck. Anyway, there was this strange looking child and as with Down's syndrome, everything was wrong but nothing very wrong. Well it was worse than Down's syndrome and so I thought, I did actually think this is what a Trisomy ought to be like, so I could claim to have made a diagnosis of 'Trisomy of an unknown nature', so I was just developing this skin biopsy procedure and didn't like to do it until I had had a bit more experience, which was largely on my knee which seems still unscarred after multiple minute biopsies, but it is very, very simple taking these small skin biopsies, but I didn't like to do it on this dying child. So I said I will rush up and as soon as it is dead and has an autopsy I will rush up to the autopsy. And unfortunately they had just given it a blood transfusion, which there didn't seem any obvious clinical need and didn't improve the typing

afterwards and I took some hand prints in great detail, and so I went back and the next thing I knew it had died and Friday afternoon was the autopsy, and it was foggy and miserable and I was driving up to this autopsy, which of course was done beautifully by Hugh Cameron, and I thought in my ignorance to take a bit of tissue of everything. So I took double samples of everything and then I drove back to Oxford and gave half of it to the person who was doing the chromosomes there, but in fact I knew that probably it wouldn't do very well because of very high infection rate in cultures, and the other half I rang up Charles Ford on Saturday morning and tried to talk him into doing this, and he said well he would go and see David Harnden, who was living in a small single prefab, a little sort of a thing like a large static trailer park, well I suppose there are still some around.

PSH. Oh yes.

JE. But living in a prefab or similar structure anyway, without a telephone or a car. So anyway, Charles Ford was persuaded to go and see him and he agreed to come out. David and Charles agreed to come out and break their 5-day week at Harwell and come into the lab and see this strange claim that I had got an interesting specimen. So there were all these little tubes I'd got, with all sorts of things marked with tissues and David set them all up, and the winner was lung. I have never heard of anyone growing lung, but anyway in 10 days David had the most beautiful preparations and the Oxford ones all died. But I was never forgiven by Stevenson for this because it was very disloyal to go to what he regarded as a rival organisation. Anyway that was interesting. It was actually diagnosed as Trisomy 17 by our experts and I remember saying to Charles, shall I go and get the parents because they all look the same to me. I had never seen cells before; they were beautiful chromosomes of course. I had hardly ever seen any before but their view was it was 17. Charles with his usual generosity, didn't put his name on the paper, because he thought David should get full credit; I think I deserved some credit, but I must say we had a lot of hangers on who had done nothing at all, let's say, except to make sure their name was on the paper. Hugh Cameron certainly deserved it, because he did make a lot of practical points and so on and made some very sound observations which are based on very large experience. Anyway this eventually got published and as Trisomy 17 I think. So it was and still is an interesting condition I think.

PSH. I am interested especially that you suspected it was some autosomal trisomy before you had the chromosomes, which was . . .

JE. Well that was beginner's luck I suppose, but it wasn't very difficult, because I mean, the botanists had got these things sorted out and the thing was, everything was a bit wrong and there are very few conditions I think which aren't chromosomal where everything is a bit wrong. I mean there are other Mendelian bony things, but when you look at them obviously they are bony things and given the fact that the bones are all messed up the rest sort of follows and the bits which . . .

PSH. But I don't think it was entirely beginner's luck John, because when I was talking with David Harnden, he said that just about all the other things

which were sent to him after that by other people turned out to be entirely normal.

JE. I don't know about those. They weren't published.

PSH. And he felt that you had had the insight to spot that this case, out of lots of others with abnormalities, might well be a chromosome abnormality.

JE. Well I think I wasn't too good on Amsterdam dwarfism. It should be the person's real description of it, whose name I'll remember in a minute.

PSH. Cornelia De Lange.

JE. Cornelia De Lange. Very brilliant woman, paediatrician who wrote extremely well on it. I think she was Dutch and wrote in French, which is difficult, and really deserves it to be called De Lange's syndrome I think, because it was very specific again and very interesting indeed so that was one of my misdiagnoses and it has only recently been discovered actually because that is quite an obvious thing where everything is disturbed

PSH. Yes.

JE. In a very interesting way. And one of the tragedies was that I would take palm prints I would take the trouble and put the initials on. When I got back I found that I had seen two babies and they both had the same initials.

PSH. Oh dear.

JE, So I had to throw them away. But of course if I hadn't made that mistake Penrose would have been really even more excited because it is the only condition in which where you get, it's absolutely diagnostic. There is no other condition that you get 5 whorls, it is almost unknown in the real world. Penrose told me that Pirie's son had these not whorls, these 5 loops. But I have occasionally seen up to 3 in normal adults, including Wigglesworth the paediatrician had 3, but it still is very interesting and very, very specific.

PSH. I was told that Penrose was very disappointed that the Galton was not involved in the discovery of Trisomy 21 and I wonder whether that was something that you sensed. It was Marco Fraccaro that told me.

JE. No I think it was only right that he should have been, because of this interesting rather high-grade patient with Klinefelter's and gave informed consent. He was just a normal man. He must've given informed consent for a testicular biopsy and another person he got a testicular biopsy from that was really informed consent I'm sure. But cytogenetics was always very difficult and was not very clearly defined and so it was very distressing. I remember arguing with Hamerton about this because they practically met on the doorstep, some big translocation family and I rather criticised Hamerton and I said surely you are not going to pursue this but they took the view that this was all sort of fair and it was a race for the gold. It seemed to me quite improper to deprive Penrose with his vast experience of this condition and at

last he had managed to get some, I think he himself actually learned how to do chromosomes and to find out how to do chromosomes, was very helpful.

PSH. It seems to me that the key thing was that people like Charles Ford had the technology for cytogenetics whereas it never really reached it at that point of the Galton.

JE. Well there was no one to do it there until Penrose literally taught himself how to do it. With Delhanty, she was probably the dominating person who got it working. Penrose was pretty good with technical things once he got down to them.

PSH. Can I come to another discovery of yours now, the X-linked hydrocephalus. Am I right that you were now back in Birmingham after your time in Oxford?

JE. Now let me see. Oh I know how it was initiated. I must have been in Oxford and I heard about the Institute at Birmingham and I had a letter from a general practitioner up near Hereford stating this and he thought I might be interested and I was. So I went up to there, and saw these children who were obviously the same condition. These two very rather backward children with rather unusual features including this thumb condition.

PSH. Were they part of a big family?

JE. Yes enormous family which extended to the Vice Chancellor of Birmingham, an Antarcticist. I mean it was really an enormous family covering all social grades and everything. Then I came across a family locally in Northampton which had six children, numerous children. This again had gone back quite a long way. In fact he had got back as far as the matron's maid at the maternity hospital in Birmingham who had succeeded in having produced some illegitimate offspring. Not sure one or more, anyway it all went back to her and just a straightforward X-linked recessive. But again it was interesting in the way it was manifesting. This family went on for some time because they kept on cropping up. Then another one I heard about somehow in Stepford a sporadic case but quite obvious clinically. It was a very unusual hydrocephalus because normally the skull is very smooth and globular, but this is often sort of potato shaped, it's that sort of irregularity and I don't understand why, because if the brain expands it is not going to produce an irregular skull anyway they do have irregular skulls or can do. This was an interesting boy because he had stayed at home, and was very backward but could recognise every car by its sound. It was his party trick. He would love listening to car sounds and he would get them all right.

PSH. John, after, I think it was two years in Oxford was it? You went back to Birmingham in 1961.

JE. Two years.

PSH. You went to Philadelphia didn't you?

JE. Yes, I had problems. In fact I resigned without a job and I went up to see Harold Himsworth and said “I am sorry, I can’t take it any longer. I am resigning and I am formally coming to complain about the Director”.

PSH. So when you resigned in Oxford, was that the time you had your spell in America?

JE. Yes I had had an invitation to go there but I wouldn’t have taken it up I don’t think, at least I wouldn’t have resigned. I would have tried to get leave of absence or something, but the other big thing was Jim Renwick had decided to shoot off so I had no company and so George Fraser suddenly turned up which certainly was good if confusing value as I used to have one of those 8 seater cars because they were cheaper, they used to tax things even though we only had one child. And it was almost every weekend George would ring up and say are you doing anything. Could I help with the moveI had this offer you see so I accepted it avidly and we just had this very pleasant exile, a year of exile working in the Children’s Hospital in Philadelphia in 1960-61, sabbatical year.

PSH. They had some very very good people there and people very interested in Genetics at that time.

JE. Oh yes. Well Noel Hungerford you see had just got this thing developed that was the great thing which also Malcolm Ferguson-Smith independently had developed. But it was a very unexpected result mixing up scarlet runner beans. You had to be a black-eyed bean or a scarlet runner. It is quite interesting. It is very difficult to do it in some places like Russia where they don’t have either.

PSH. David Hungerford, I think I’m right but he had died quite young?

JE. He did yes.

PSH. And he’s one of the people in the early chromosome story but I have not been able to find much out about? What kind of person was he?

JE. He was a perfectionist. He was, he had been a photographer to Life, so he was a master photographer and I had a slightly upsetting experience actually because I was asked to see a case of Down’s syndrome and I saw this case and I said that’s not Down’s syndrome. And so we looked at the chromosomes and it was an unbalanced translocation in two children and the father decided he was going to be vasectomised. So I said if you are going to do this would you mind if we nipped a bit of the testes out? He said that’s alright if its not too much I hope. And so we went down to get a bit of this and Hungerford went to do it and of course it was a crucial thing, but Hungerford decided to do it by a special method and I was very stupid although I had no experience of it, with a book in one hand I couldn’t have done worse than nothing, and so he had an adequate specimen but he did something very adventurous and unusual and by that time nothing ever came out, but he was very pleasant. He lived quite a long way out at a place called, I’m not sure where it was, a big research place anyway, about 5-10 miles out. So he was

very highly thought of, but got some nasty rapid neurological disorder, I forget what it was. He seemed alright when I knew him.

PSH. And Peter Nowell was a haematologist, is that right?

JE. I think he was yes. He wasn't all that wildly interested except as a blood thing, it was interesting nobody's seen, he couldn't have been a haematologist because there was so much nonsense written about what kind of cell it was. Well he didn't know what kind of cell it was. It wasn't a big problem what kind of cell it was.

PSH. And who else was at Philadelphia at the time. There were some others like

JE. Well there was one Bongiovanni who was a great expert because that is how I got involved I think because I had a lot of experience with adreno-genital mainly because Hubble was a great expert on this and we used to see all these which of course were usually rather mild. I mean the idea that it was a terrible condition and you must rush around aborting everybody. But most of the cases are in fact fairly mild and now easily treated but he had large numbers of these and I think it was because I once drove Bongiovanni back to Hubble where he had given a lecture at Oxford and he offered me a year in America which was on the way driving him back to Oxford so I, with a bit of correspondence, I accepted it and that was very enjoyable. And also I used to go up about once a fortnight I think to New York on the train for a very interesting meeting by Levine on general genetics with a mathematical flavour and then several times I went to see Victor McKusick.

PSH. Was that when you got to know Victor McKusick first?

JE. Yes I think he invited me down there and asked me to give a lecture or something and heard David Weatherall was there and so it was a very interesting department.

PSH. That was when David Weatherall was doing the fellowship?

JE. I suppose something on it he was doing. Yes he was very thrilled. He had managed to hybridise dog and man with the haemoglobins and was really excited about it.

PSH. Then John, you came back to Birmingham and then . . .

JE. Curiously enough you see when I had been two years in Oxford, which was rather a waste of time in many ways, very disturbing. It was very expensive. It took a long time to get financially solvent because you sell the house, you move house, you move your family and they weren't educable at that time but still there were two of them and you get yourself established and Felicity was trying to do some work as well and that was disrupted. And everybody seems to be alright in Oxford. It's a nice place to live and you know pick a great department and when this offer came up and I was invited, Pickering's department in Oxford it couldn't be a better place to be and when

you end up and you get there and you find you are going to be in a field, they are trying to build a hut which is rather small and then . . .

PSH. Yes that's not easy.

JE. And then they find something and you agree you are not going to have statistical people around and you then find that there are 4 computer desks for left-handed people, which is an error, so it was obviously arranged for a whole lot of these computer people. I had a funny experience with him which was rather traumatic but I mean it was impossible because he was answering parliamentary questions in the MRC and one came through to him. There were 120 cases of anencephaly in Scotland this year since some bomb went off or something and there were 110 cases 110/140 that sort of number. So is the Minister aware of this increase or something. Literally the question was, is 120 bigger than 90 you see. So Stevenson came towards me and said can you tell me the kind of question they want if 120 is bigger than 90? And I said well there's nothing you can do about this except say "yes". He said 'Well that's not what I wanted. I wanted chi squared and things' so I said well did the Minister want, was the question about chi squared? If the question was "is 120 bigger than 90" there is no way in which I could give an opinion that it's not bigger than 90. And so he went off in a great huff and he came back. Well that's the sort of thing I wanted and he had a letter from Cheeseman saying oh dear nothing to worry about, chi squared is 3.81 or something.

PSH. So to come back to your return to Birmingham, how long was it that you were there before they made a chair for you in Birmingham?

JE. Well McKeown always had an empty place. At that time he would always try to keep a lectureship empty in case he wanted to invite somebody. Professors could do that then of course but now you can't. I mean they had a Professorship in genetics here just after I left available and they advertised and they got a whole lot of people and they were very worried they wouldn't get a good person and so they agreed that they would ask one question which was non-negotiable, if it was wrong, and they asked what a recombinant was. They all got it wrong. And they were all rejected. But McKeown always kept one vacant and he hadn't filled it so he was just able to invite me back instantly. Of course the other problem I had, I was verbally offered a salary but when I got there it was much less. And the same thing happened to, so I complained about this rather modestly and was told that, the administrator wrote back to me and said I am sorry the salary isn't what you thought it would be but Dr Stevenson had no authority to offer this salary. So that was why I moved. What do I do now. Do I write to Sir Harold Himsworth or do I consult a lawyer and Sir Harold decided that it should be increased to what was excessive. It was £1,400 rather than £1,200. But it is quite a difference. Anyway I went back to Birmingham (in 1961) and I was very happy there and there were no problems. It was a very casual job. It was very nice of them to organise it because it was split between McKeown's department and Hubble's. It was a split without any formality. It was all very odd. And then a Quaker came and wanted to give some money and they built a nice little Institute which became virtually part of mine. At least I was able to design it the way I wanted it and everything. This was going to be the connecting link between the Maternity Hospital and the Children's Hospital and this would

have been absolutely wonderful, but for various reasons with strikes and things, the whole thing sort of fizzled out and it was very, very sad because the space was there and they could have had, and this was going to be the link. It was a wonderful opportunity, but it all fizzled out and when I was actually offered to my extreme surprise a chair and moved to Oxford I accepted it, but I think if this had gone on and it was intended and it was really being on the umbilical cord . . .

PSH. Yes that would have been a wonderful opportunity

JE. Oxford was very strange. The big things about Oxford were David Weatherall's work on haemoglobins and Harwell. Nothing else seemed to be happening, except super plant cytogenetics and that sort of thing, but I didn't see there was anything going on. Superb work of course on the complement which I hadn't even heard of then I'm afraid, but a very fine Professor of Biochemistry was Rob Porter, a complement expert and a very fine leader.

PSH. What year was it you came to Oxford?

JE. '79.

PSH. '79. That kind of leads me now to the Oxford grid, which presumably did arise out of all your links with Harwell, and when did you start thinking in terms of putting the mouse and human linkage into that form?

JE. Well that form actually was first devised by me in 1977 to relate at a meeting which Walter Bodmer organised for HLA and I was working a lot on HLA in Birmingham. I had to give it up immediately I got to Oxford because it was too confusing, particularly with the transplant surgeons and people. But I was really working quite a lot on it and I was doing all the sums and the documentations for the surgeons. I had a very good relationship I found. All the work was being done by Pauline Mackintosh and a very fine system and also I was working with David Harnden, but I have always worked on the principle that we split the spoils and write single author papers, so people don't realise how privileged I was to work with David Harnden for example. We had a very harmonious but I did all the clinical work for his work, his telangiectasia ataxia, which was very interesting, but I just didn't want to be involved because I would never write a paper if I could not answer questions on the subject of the paper, but his papers were beyond my continental shelf and that seems to be the first thing, and he was so helpful in giving advice and growing things and had a very good department. I am sorry, I was off the track as usual.

PSH. That's alright. So the Oxford Grid?

JE. The Oxford Grid, yes that was first used in 1977 comparing the beta locus and what was then the B and D loci in HLA and they were ideally suited to it because you got the proportions and the spots and so on so that's when it all came out . And then I thought well that's the obvious thing to do. If you've got any two things and you've got a grid, the thing is not to have squares but to have rectangles which are meaningful. So it was exactly the same thing as the 1977 paper, which I only found the reference to - you've probably got the

reference, I only found the reference to it about a month ago so I don't think it was mentioned in the Oxford Grid paper I wrote. But it did seem a good way of doing it and then it was a good time to get this homology worked out I thought. We had a wonderful time because every month in alternate places we had this meeting and I did most of the writing actually, of course it was all heavily checked, particularly by Mary Lyon but I said I really can't cope with worrying about the authorship; is the alphabet alright? The first one was rather funny because there was a PhD student and also a very attractive Italian girl also a PhD student. They combined activities, not very productive to their thesis and Ian Craig, who is very astute in these things, said to him well I don't think you are going to get a PhD. You lack the aggressive interest in the unknown. So I can't really recommend you for a further year but we do need somebody around the department who knows about computers and is reliable and so on, so we can offer you a job which you fix with me as well, sort of half time with the computers helping people with them and half time with technical work. Particularly we had the problem of a high IQ rather lazy unreliable technician I had inherited in India who really was a liability because you couldn't rely on him keeping the liquid nitrogen. All our capital was liquid nitrogen. So it was terribly important to have somebody who would really be reliable and keep liquid nitrogen going and work on Sundays and that sort of thing if need be. I remember in alphabetical order, so he came first of course. Next thing I know he is wanting a reference for a job, rushed off to his girlfriend in Italy without a job. Then he found that IBM was offering a job so he asked for a reference. I was able to give him a super reference with Dr Mary Lyon FRS and all these authors and so on and he was the first author. But I think in no time at all his salary made that of the people who had succeeded in getting a PhD. Shame. I have lost touch with him.

PSH. Who were the people then involved mainly at the Harwell end, apart from Mary Lyon?

JE. Well it was really dominated by, because he had been interested in comparative mapping. He had written very key papers on comparative mapping in albinism. Tony Searle. So he was the dominant person who did most of the work. In fact the next paper we had was Buckle et al and that had the key thing for the X chromosome. The X mouse chromosome that Mary Lyon's work with this came in and that absolutely dominated the whole paper.

PSH. Was Veronica Buckle at Harwell or Oxford?

JE. Oxford, yes.

PSH. John could I finish up by going more or less back to the beginning and talking about your simulation of Mendelism paper, because that is one which I have always felt is very important and it is right back in 1960, so what gave you the kind of inspiration and background for that paper?

JE. Well I think what actually happened, this was my first year in Birmingham, you know new job, new house, new baby as well, Felicity was staying with her parents in London and so for 2 or 3 months I was on my own in Birmingham and I was reading Biometrica as a sort of evening thing, so I think it was really the so called tetrachoric coefficients and the way because I like to visualise

things. Because you get these by various humps and so on and slices. I found that a very interesting concept in the way of dealing with it, and the whole Galton thing you get, father and son, the simplest one I suppose. And you get their heights and you get these elliptical grids and I got rather fascinated by that and found it rather interesting. And then it seemed to me clear that these things were very confused and so I wrote this little paper which I have completely lost and I think you might have the reference to it because I thought I'd try read it some day. Put it on to my web site.

PSH. I do have it somewhere. I do.

JE. Anyway it's in a Journal. I can get it out of the library but I don't have a copy of it. I might try and photostat it someday. The thing is, this of course wasn't original, I did actually point out to give the reference to Pearson's work but I didn't give the reference to Penrose's work or to Sewall Wright's. Penrose wrote a similar paper without giving reference to Sewall Wright actually but he must have known the work, probably so well known he didn't bother.

PSH. Did Penrose then, he must have seen your simulation?

JE. Oh yes he did and he was very kind, because we had this 1969 issue of the British Medical Bulletin and I put a paper in on that and gave the reference to Pearson but I didn't give the reference to Penrose because I didn't know about it and Penrose was terribly polite in the reference right at the beginning of the paper, and it wasn't until later that I discovered you know all this Lambda business. People keep writing about Lambda and you must find out the relative excess, the degree of familiarity so to speak before you rush around doing these sib pair things and so on, well Penrose pointed out that this was complete and utter nonsense. In his first paper on sib pairs, which no one seems to have read, he used Lambda in a quite difference sense. So nobody who uses Lambda in sib pairs has ever read his paper unless they were intending to be disrespectful and stealing a parameter and misusing it. But later on Penrose wrote about what he called K which is what people like Lander and all the sib pair people call Lambda, and he pointed out again exactly the same as I have done but being Penrose it was rather more clearly put and acknowledging, well it was before my paper so he couldn't acknowledge me, but acknowledging Pearson and pointing out that it was virtually formally irrelevant so all this business of what is Lambda and the thing is actually formally irrelevant so this isn't the only un-read paper. The other papers, Penrose's paper on sib pairs is virtually un-read, particularly by people who write about sib pairs and so of course are the papers of Cedric Smith and Cepellini on haplotype, where a haplotype of course is formally impossible to turn a phenotype into a haplotype and these things were all so well, clearly expressed in the earlier days. So I sent that paper in for the meeting in Canada, but due to some muddle which is my fault I suppose, it never made the grade but then somebody didn't come and somebody else said well I'd got a paper which was late or hadn't got a grade. I would be prepared to give it if so and so couldn't give it at the same time. So I stepped into an empty slot and naturally gave the paper in there and I then gave it again in New York where Waddington was present and was very polite. Just

after a lot of people sort of drifted off to New York and I just happened to be in the great centre of the work in New York which was quite interesting.

PSH. And that was 1958 and I think it appeared in Acta Genetica Statistica in 1960.

JE. Oh yes. Did it? Well it was all very slow.

PSH. I will check it afterwards.

JE. Very slow about these. There was no rush.

PSH. But I am interested . . .

JE. Acta Genetica Statistica was it?

PSH. Yes.

JE. Well I can find that somewhere I suppose.

PSH. I'll find it for you but I'm interested that it was already, so to speak, prepared in 1958.

JE. Yes it must have been yes.

PSH. John, I want to finish in a minute but I would be grateful for the record just to ask you the questions that I have been asking everybody else and the first is, is there a particular person that you feel had an especially strong influence in terms of your career in genetics? Would you say there is one person or is it… ?

JE. Well there are several I can think of very strong influence. I think the strongest influence is during the war, when I was 12 or that sort of age, when we had to work on the farm and I used to wander off to our friendly farmer who had about 10 cows and that was his total assets, and he was a very intelligent man and he used to tell me harrowing stories about book farmers, and so I was very impressed I think with his harrowing stories about book farmers, who would come and give him advice on matters on which they knew nothing and then later at my school there were one or two masters who were fairly influential. When I got to Cambridge, I think one of the most influential persons was J W S Pringle, partly because I did zoology and he produced really superb lectures. A superb department, the best lectures I have ever come across was in the zoology department. They have eclipsed anything I have ever come across in university lecturing, but quite coincidentally he was the president of the glider club which he'd sort of built up. He had quite a distinguished career. He was in the middle of his PhD when war broke out, trying to listen to a cockroach by using electrodes and things with an enormous box with about 10 valves in to amplify what a cockroach did when it scratched. Doing sort of Sherrington work, the Sherrington of the insect world, but he was very influential during the war because he got radar effectively working on flying boats which had a very major effect on the u-boats' behaviour, because they couldn't casually come up at night and expect

not to be seen. So I was very influenced by him, particularly with his direct approach to things and then I was very privileged I think in the several people I came across clinically. And what impressed me most of all, as with great lawyers I am told. Their judgements are right but their reasoning is wrong and I was very impressed with how incredibly confused really able physicians were if you asked them how they reached a diagnosis. They either said something that was muddled or they said something that was wrong. But they are the sort of people I would go to if had . . .

PSH. Yes, they got the answer right?

JE. And so I was really impressed with this power to do this, and the other thing which I noticed is this high correlation with innumeracy and it wasn't just Darwin and Bateson who were innumerate but all sorts of, not to mention Faraday of course; numbers is a great handicap because mathematical things depend on a lot of things to be equal which never happens in biology. So if you think of things mathematically you have to abstract it in a way which Darwin felt, if only he knew numbers. Well I felt that innumeracy has an enormous advantages if you have the equivalent IQ and not led astray by mythical approaches and wild schemes and of course what is a problem in biology now is that people who do the sums are not the people who know what the thing is and so.

The worm is interesting because the intellectual leaders in genetics seem to all work on the worm now, including my successor, and what is also interesting about the worm is that it has been dominated by the very interesting way of drawing or computerisation called ACDB and so it has virtually replaced numbers by diagrams
and they are so much more powerful and also they don't give judgement. The thing that one does not want I think in a complicated thing is to have significance tests and M Lods and all these things, because if you take these things that have been done like hapmap and so on, if it's a genuine thing, it is not going to be significant but it is going to be interesting. So the fact is if there is going to be a little sort of pimple as with diabetes in the early days there was a little pimple of insulin. Well there was a learned paper from statisticians who rejected it. Wasn't quite good enough but a priori one might expect insulin to have some connection with diabetes and so it's very disturbing I think this fact. If you take now, you see numerous advertisements appearing almost daily, biomathematician wanted, a position in biomathematics etc, all those statistical departments and it usually says you must do 'A' level this and that and have experience of mathematics or computing or something and no knowledge of genetics necessary.

PSH. No.

JE. And really what you need is, geneticist wanted no knowledge of mathematics necessary because we can teach that in 3 months, but they can't teach medicine or genetics out of a book.

PSH. John, just to finish off, which piece of work, or I can allow you 2, which of your pieces of work do you feel most proud of, thinking in terms of leaving for posterity. I will allow you two.

JE. Oh. I don't know. Hoping my paper about to come out on hapmap will occasionally be read, but the trouble with that is long-term posterity.

PSH. Thinking of things you have done already, back in the past.

JE. Well I suppose the first paper, which I can't find but you know where it is, is probably a potentially influential . .

PSH. Simulation of Mendelism.

JE. It was in 1969, the British Medical Bulletin had a more extended version which perhaps should have been rather better written with more experience and clinically I suppose the biggest thing I have added to is to produce things. I have produced these minute skin biopsies which were so simple that you didn't have to be medically qualified; a mother could watch without being upset and also when I started we had twenty ml of blood and when I ended we were doing it on capillary blood. So I think simplification of cytogenetics, that's all I could do was simplify, I very much regret I hadn't moved in to find these bands because it was so stupid. It was obvious that one could to do it, but like everybody else it wasn't worth looking for bands. You couldn't have bands because the DNA was all the same and so the bands, the biggest mystery in cytogenetics is what is a band?

PSH. John, thank you very much. I will stop the machine there and thanks very much again for giving so much of your time.

JE. It's a pleasure to be interrogated in a way which makes one think about things.

End of tape