David Hopkinson

Personal Details

Name	David Hopkinson
Dates	Born 1935
Place of Birth	Chesterfield, UK
Main work places	Galton Laboratory, University College London
Principal field of work	Human Biochemical Genetics

Short biography

Studied biochemistry and medicine in Cambridge and London, followed by work in Medical Biochemistry in London with Professor Harry Harris, moving with him to the Galton Laboratory and succeeding him as head of the MRC Human Biochemical Genetics Research Unit. His principal research field has been the genetic variation of human proteins.

Interview

Recorded interview made	Yes
Interviewer	Peter Harper
Date of Interview	06/04/2011
Edited transcript available	See Below

Personal Scientific Records

Significant Record sets exists	Yes
Records catalogued	Yes
Permanent place of archive	University College London (with related records of Galton Laboratory).

INTERVIEW WITH DAVID HOPKINSON, 06/04/2011

I = Interviewer (Peter Harper)

H = David Hopkinson

I **It's Wednesday April 6th 2011, and I'm talking with Professor David Hopkinson at the Royal Society of Medicine, London. Can I start off by asking just where and when you were born?**

H I was born on the 26th June 1935 in Chesterfield, Derbyshire. And I lived there all of my school life and went to school there.

I **Yes. Can I ask: were there any members of your family who were particularly involved with science or medicine that gave you a leaning?**

H Not at all; no.

I **What did your dad do?**

H My dad worked in the iron and steelworks across the road as the foreman in the rolling mills. My mother was a dress maker, though her parents had had a fruit shop in Chesterfield, but her father died with the influenza epidemic just after the First World War. My dad was in the First World War and I was a fairly late arrival to the family; my brother was 10 years older. He became a school teacher.

I **Just the two of you in the family then?**

H Yes.

I **What about the local schools in Chesterfield? Did you go through primary and secondary school there?**

H I went to primary school, yes. My mother made sure that I moved from the local primary school because she didn't think it was much good; and then I moved to a primary school with another friend and we both used to walk to this other school and we were both scientifically inclined; he became a pharmacist. And we grew up together and then we went to grammar school together. He was a little bit older than me and he left school in order to be an apprentice pharmacist in a chemist shop while I carried on through the Sixth Form. And then while I was in the Sixth Form I decided that I would like to do biochemistry because I thought this sounded like a very interesting subject, and I'd read Ernest Baldwin's Introduction, I think it was, to Comparative Biochemistry, which believe it or not was in the Chesterfield Town Library, which I think is quite remarkable. [laughs] And I thought, "This is really interesting." So I spoke to my head teacher, headmaster, and he didn't really know what biochemistry was and not many people seemed to know what it was all about at that time, and suggested that I should perhaps do a medical degree, "since there's a lot of biochemistry in medicine"; he thought it would be a good grounding. And then someone else suggested that perhaps I should go to Cambridge, which is then what happened. I got a place in Cambridge and so I did the Natural Sciences Tripos and then, in those days most of the medics left Cambridge and came down to London. And I went to the London Hospital Medical College, and then finally qualified in 1959; did the regular house jobs for a year there, and then thought I'd like to return to biochemistry.

I **Can I just ask at this point: I mean, reading Baldwin's book when you were in the Sixth Form, that was kind of unusual, quite apart from the fact that it was in the library. Did**

you have any particular teacher who inspired you a bit?

H We had some very good teachers in the Sixth Form who encouraged us in botany, for example [Mr. Elgar], to look at the wild flowers and collect the flowers from the crop plants, and things like this, and round about in the Peak District. And we would mount those and investigate them and so on. We also had a greenhouse which was built whilst I was there for us to grow things and study the physiology of plants, and to some extent, the chemistry. And then we also had a very good chemistry and zoology teacher [Mr Cook] who encouraged us to do a lot of dissection and a lot of, quite a lot of, work at home by taking animals home and dissecting them; things like earthworms and fish of various sorts. Dogfish classically used to stink out the shed. But fish that was available on the market and stuff like that. And also we, I was very fortunate in my final year in school, because another friend [Simon Harcourt Webster] who was going to go to Cambridge, his older brother had gone to Cambridge to do medicine, to Emmanuel College, so he knew all the ropes about doing medicine and said, "We should do Part 4 of the first MB, which is organic chemistry. And if we do that here at school, we should be exempt from it when we go up, and we can go straight on to biochemistry."

And this sounded wonderful; wonderfully appealing to me, even at that stage. And so, as it happened, during that term the chemistry teacher was ill and was off school so we got permission from the Head to work alone in the chemistry lab when it was empty. So we set each other all manner of organic chemicals as "spots" to do analytical organic chemistry, which of course wasn't part of the A-level syllabus. And so we were doing, essentially we were doing qualitative analysis on organic chemicals, which you'd normally not do at school; and that gave me, it gave us both, a lot of independence in the lab. And I saw this friend just a few weeks ago, I was chatting to him on the phone afterwards, and he was reminiscing about that he never felt more on top of his chemistry than at that time. And it made me very confident to be in the lab, I think, because we were doing things that we would never have been given on Health & Safety rules, to analyse safely and not have any explosions, and so on.

I Did you have any disasters or explosions, or were you -

H We did have a few… we had a few moments of investigating rather toxic lachrymatory chemicals, for example, which were quite a challenge. [laughs] And so we both sailed through, we both sailed through the Part 4 Organic Chemistry exam, because that involved not only exam paper but also a practical exam up in Cambridge. And we were both then able to go straight on to do biochemistry in our first year.

I That's very fortunate.

H That was very fortunate. And then I went to the biochemistry lectures every year for the next three years, because they were, I would just sit in because I was so enthusiastic about them and enjoyed them so much. Obviously I couldn't do the practical work that they were doing each year, but every year there was something new coming so the alpha helix and the beta pleated sheet structure of proteins were just coming along at that time.

I Remind me of the year again when you started at Cambridge.

H 1953

I Well, that was a rather fantastic time.

H Absolutely; yes. And then of course the DNA story was beginning to spread around and, as I say, secondary features of protein structure were just beginning to come out. And also we did quite a lot of enzymology, and the interest in enzyme kinetics and stuff like

that was very significant.

I Who were the main people at Cambridge at that point? I mean, I'm familiar with the MRC Unit and people like Max Perutz and others, but what you might call, in biochemistry.

H Yes, in the lecturing: Baldwin had already moved by then to London to University College; and so we didn't see him. But we had Dixon and Webb who wrote the famous enzymology book, gave us lectures. Webb used to bring the house down with his pronunciation of 'enzyme specificity', which he found extremely difficult and would… and in those days, the undergraduate lectures, were quite riotous, and we also had Saturday morning lectures so that, I think so that we could keep within the relatively shorter terms of the Cambridge year. And the Saturday mornings were an absolute riot; the lectures. We had one lecture in biochemistry from 12noon until 1, and people would do things like bring in their goose, or a dog or something like that. So Dixon and Webb; my own tutor, Don Northcote, was a very good plant biochemist and many others.

I Did you find, I presume that you had the age mixture in Cambridge with quite a lot of people having gone through national service first?

H Yes, I mean, I was scheduled to go up in 1955 because that was, the first acceptance I had was after national service, but because I got Part 4 of the organic chemistry, that was an extra bonus and I was moved forward a couple of years. They found that they had space in Cat's after all, so I escaped National Service. And when I finally qualified [in 1959] that was the last intake, and I would have been in the very last intake except that I had significant and sufficient trauma to one of my knees, playing rugby, to allow me to get out of it. [laughs]

I That's good because to be in the very last intake would have, kind of been frustrating, wouldn't it?

H Absolutely. Absolutely, yes.

I So you did, I mean, I never quite get my head round the Cambridge structure, but Part 1, you did biochemistry?

H Part 1 was the Tripos, yes. And in those days most medics did Part 1 [Anatomy, Physiology, Biochemistry, Pharmacology, Pathology] and that was it. I was asked if I wanted to do Part 2 and I, for some idiosyncratic reason, said I thought I'd like to do a Part 2 in Psychology. I was quite interested in psychology and it seemed to be a very interesting line at that point. But my tutor [Bob Comline] in 'Cats', in St. Catharine's College where I was, didn't think this was a very good idea, and so he said that I should concentrate on getting what was known as the "qualifying exam" for anatomy and physiology out of the way instead; and perhaps get a scholarship, try to get a scholarship for the medical school that I was going to go to in London. There were only two people in our group that did the Part 2 of the Tripos, at that time, and the others in my college, I think, 6 from 8 of us just did, essentially did the Part 1 over 3 years. And, so that's what I did, and in fact I did end up getting an entrance scholarship to the London Hospital Medical College and I went there. It didn't make any difference financially because I'd already got a state scholarship which was just simply substituted.

I Yes, those were different days.

H Aren't they different? Amazing.

I Okay, so at the London: that must have been quite a contrast for you, coming from the North, and the East End and everything. May I ask, did you live around the

London Hospital area or -

H No. In fact, we were a very close knit group; there was a close knit group of about 6 of us from 'Cats'. One person who was in our group actually decided to stay on in Cambridge and he never left Cambridge, and remained doing research in Anatomy for the rest of his life. But the other medics: a couple went into halls of residence; one at Bart's and one at Westminster; the other 4: one at Mary's; one at Guy's; myself at the London; and another at University College: decided to live together in a flat in Earls Court, which was great. And we were, we felt that we would enjoy ourselves away from the surroundings of the Medical Schools. We'd had a lot of rather cloistered life you know, in the Cambridge College type of accommodation; and living in a hall of residence in Whitechapel or Guy's or whatever, didn't appeal.

I No, I can absolutely sympathise with that. Cambridge, or for that matter, Oxford, are very nice places but you know, 3 or 4 years -

H We were glad to get away.

I Get into the real world.

H Yes. We were glad to get away. I enjoyed it enormously; I thought it was a wonderful experience. But the idea of staying there in an academic position didn't appeal at that stage. And I very much enjoyed the London and its position and the people who were patients in the London Hospital. The thing that happened to me, of course, I still had my North country accent, with the broad A's, and I soon realised that the people in Whitechapel were finding it difficult to understand what I was saying. So I just gradually lengthened my, you know, changed my speech pattern so that I could be understood, and then just did the ordinary house, not house jobs, the ordinary clinical course there.

I Did you find your biochemistry went a bit underground during the clinical years, or did you manage to make links as a student at the London that kept it alive?

H No, it really didn't, I didn't do any independent practical work during that period. I didn't make any lab connections, unlike Peter Cook, for example, who came on after me at the London. But Peter was always interested in blood groups and did some blood grouping on the side and made some connections there with Barbara Dodds, serologist, in the Pathology dept at the London Hospital. Peter was also always trying to do LOD scores and stuff like that. [laughter] So in that respect, I didn't keep those connections until, I became interested in the, you know, the clinical chemistry, I suppose it was called in those days; and chemical pathology. And then one of the final year courses we had as undergrads, as medical students, at the London Hospital was a course that Harry Harris taught on chemical pathology.

I I was going to ask… so Harry Harris was already at the London?

H He was at the London then, and so I went to Harry's lectures and I chatted to him a bit; nothing particularly, nothing over the top. At that stage he was actually just on the verge of contemplating a move to Kings College London. And by the time I'd finished my house jobs, Harry was leaving the London and going to King's. And I went to see Willy Warren who was the head of biochemistry, at the London, to say, "Is there any chance that I can come and work in the lab?" I think I didn't know at that stage that Harry was leaving, and so I said, "Is there any chance I can come and work in biochemistry?" And Warren said, "We've got space because Harry Harris is leaving and you can use the lab space that he has, and also you can perhaps teach the chemical pathology course." [laughs] because he didn't have a medic to do that course in his setup. So I was signed on there for my first job, which was like a junior lecturer post for a year. And that was, that allowed me then to do two things, really: brush up biochemistry and to get back

into the lab, and of course I found out all sorts of things that I'd not come across before; stuff that Harry had left behind like… I was aware of the technology associated with the amino acid chromatography but I'd never actually done it myself or seen it. And so I was able to do that kind of, get working on that myself, and also a little bit of electrophoresis.

I What year have we got to?

H We're into 1960 now. 1959 I qualified; 1960 summer, I went over to see Willy Warren and he said I could do this lecture course for him, and also teach in the student practicals for biochemistry.

I Were you at any stage, I mean, were you always clear that you wanted to do lab work and medicine, rather than clinical patient-related medicine?

H I did enjoy very much the interaction with patients but I was really more attracted to understanding how things worked, and you know, how things could go wrong. And how one might be able to do something about it in diagnostic terms by developing procedures and tests and so on. And also just finding out more stuff about things. I can remember having a bit of an idea whilst doing obstetrics; I was very intrigued by what was in cord blood, and what was the composition of that umbilical cord, and why was it like that? I can remember talking to one of the medical professors, I didn't just go and talk to Willy Warren in biochemistry, I did actually go to the senior people in the London, including the head of the Medical Unit -

I Who was that?

H That was Clifford Wilson. He was a big name in renal function and electrolyte balance, and in those days they used to classify patients with Type 1 and Type 2 nephritis; Which I think, turned out to be E coli infection related. I said that I thought cord blood was quite an interesting area and something I would find interesting to investigate, and he couldn't really see it; his brow was furrowed when I suggested this as a possible little research project.

I also omitted to say was that, at this time, one of Harry Harris' people was still at the London waiting for a lab space to become ready at Kings. And that was Mary Whittaker. And Mary did a lot on cholinesterase, and indeed was affected by cholinesterase poisoning herself.

I I didn't know that.

H That was the reason she had a limp and she'd experienced exposure, I think, when she worked for ICI. But she was, because in those days, we didn't have recording spectrophotometers, you just had this; you had to do it all by hand and pull levers and things like this. And so Mary was like the Queen of the Hilger spectrophotometer, doing these dynamic enzyme activity assays for human serum pseudo-cholinesterase, and also studying the effects of various inhibitors; so qualitative analysis on top of the quantitative analysis. And that was the first, I suppose, signal to me that this was an area that one could exploit: instead of just measuring things, just in simple quantitative terms… If we could do qualitative analysis as well then that would be a way of doing it and going further

I So how long were you at the London in chemical pathology?

H About eighteen months. I thought about the possibility of going back to Cambridge and doing a Part 2 in biochemistry, and I got in touch with Comline, my former tutor and he made various enquiries, and the timing of it was just a little bit wrong, because I was finishing my house jobs in, yes, I finished a house job in September; September 1st I

probably started, so I finished on August 31st 1960, so I was just a little bit too late to sign up to Part 2 biochemistry for the current year. And, but he spoke to, hmm, I've forgotten the name of… I think it was the chemical pathologist at Guys who suggested that I should do a diploma in Chemical Pathology at the Hammersmith Post Graduate Medical School, and so that … I did consider that, and all those things were in my mind, and I was discussing this with Warren, and also I was discussing this with Harry Harris, because I'd been over to Kings via an introduction of working with Mary Whittaker, and we did some quantitative work on haptoglobins, to see whether there was any difference in the haptoglobin level according to haptoglobin phenotype, the 1-1, 2-1, and 2-2, which were the 3 common variants.

And haptoglobin levels were increased in some inflammatory disorders, and so I got quite a lot of lab experience from those sorts of procedures, and you know, finding yourself needing to know the concentration of hydrogen peroxide in this bottle and not quite knowing, because you've got to titrate it, was a very important lesson again, and discipline in laboratory techniques. And Harry also became aware that I was doing things like electrophoresis of the cholinesterase, and trying it in serum cholinesterase; and I was first of all doing it on these cellulose acetate strips, and using this technique of, histochemical technique, which is directly lifted from a histochemical account of staining cholinesterase in sections {see lab note books].

I So these lab books are from that -

H Those lab books are from that period, yes. This is August 1961. Yes.

I Fascinating.

H So I would take these things over to Harry and he would, of course, Harry was a great enthusiast; he'd make you feel as if you'd solved the problem that everybody else in the world wanted to know the answer to. And so, and then I ended up going over there to King's more and more often, and sorry,…. after I'd been there for a year, not quite a year, I said to Warren, "I think I should do the chemical pathology course at Hammersmith , and I think in order to prepare for that I should probably leave you in June or July and apply for the post of resident pathologist at the London Hospital" where I would be doing the kind of laboratory work that was relevant to the course. So Warren agreed with that, and I agreed to carry on teaching the chemical pathology course for him, which I did for the next 10 years. I worked then as a chemical pathologist at the London, and that involved working during the day over at Kings, and doing the chemical pathology, the resident pathology work in the evenings and at nights, when I was on call at the London. So I did quite a lot of lab work then over at Harry's lab as well as the resident pathology stuff. And the cholinesterase work, the electrophoresis of human serum cholinesterase started in that way. And then of course Harry becomes very impatient and wanted the experiments done over there, at King's College, because they were doing starch gel electrophoresis of the human haptoglobins, the transferrins and other genetic markers.

I Had Harry already set up the MRC unit?

H No, that came next. During that autumn as I was doing my first 6 month session in chemical pathology, the resident chemical pathology job, Harry said to me, "Just hold on because I'm going to put in for this Unit, and we might be able to get you onto that, and we can carry on doing this kind of stuff." So that's what happened in January. So that was when we started the, there's the first MRC Unit report. [SEE MRC Reports & lab note books]

I Oh good Heavens!

H In 1964, covering the period from 1962 to 1964.

I That is fascinating, too.

H So we continued doing this work, and by now, of course, Bette Robson was involved and Bette showed me how to do starch gel electrophoresis and we used to work together on that. And we moved forward in the cholinesterase work to be able to identify a curious type of polymorphism where some individuals showed an extra component, and mostly it was a single band. And that variant was in Nona Parry Jones, who was the senior lab technician in Harry's group at Kings. All of these blood samples [See lab note books] tended to be of our own blood or samples that were being screened for other markers, for whatever reason. And here you see TR85; that's the Tristan da Cunha Islanders; you remember the volcano went off in about 1961 or so? And the blood samples were collected from all the Tristan da Cunha islanders and then shared out amongst the blood groupers and various other people to test for various genetic markers.

I So you did the whole series of Islanders, really?

H We did all of the Tristan da Cunha Islanders, and it turned out that they had a higher frequency of this double band pattern of cholinesterase in their population, which was a good index of how powerful it is to be able to look at different groups and find higher or lower frequencies of variation. I think the Tristan da Cunha Islands samples came from Tom Cleghorn, who was in the northeast London blood grouping centre. And of course they were initially involved in case the islanders needed blood transfusions following their emergency evacuation

I Yes. So you moved over to Kings then, in the year again?

H January 62.

I 62. And what, well, I mean, from what you're saying the work looks almost seamless but it continued and developed rather than any break in it?

H Yes, Harry did a very, what I think is a very sensible thing: I was, I mean, although I feel that I was, you know, a bit of a biochemist, I was nothing compared to real biochemists [laughter] so he teamed me up with Neill Spencer, who was a biochemist and had done a degree in biochemistry, and a PhD in biochemistry, working on sugar alcohols as a matter of fact. Neill and I worked together very well and Harry had discovered in the literature; there was a lot of literature on phosphatases in those days, both in the clinical literature, things like prostatic phosphatases, and phosphatases in bone, and phosphatases in the serum and so on. And there was a report by a couple of American biochemists called Tsuboi and Hudson, who did a whole series of studies on human red cell acid phosphatase. And I think it was in the clinical chemistry literature, and they reported an aberrant pH optimum in red cell acid phosphatase in some individuals. So the pH optimum was shifted from I think pH 5.5 usually to pH 6.5; something like that. So Harry suggested that this might be something Neill and I could look at together and see if the difference was genetic.

Before that, Neill Spencer and I had worked together on a project which indicates the topicality of the Lyon hypothesis at the time. At the MRC Population Cytogenetics unit in Edinburgh, Court Brown was the director, and Harry, was a very good friend; and they suggested that we might like to look at G6PD levels in individuals with varying numbers of X chromosomes to establish whether the hypothesis of dosage compensation still was valid for triple X females, XO Turner females, XXY males, and XXXY. So that was one of the first things that we did together. for G6PD activity. And because, and working out the assays, Neill and I recognised that we had to do both,

because G6PD forms 6 -phosphogluconate; 6-phosphogluconate dehydrogenase [PGD] then uses the same coenzyme to go to the next stage, and so we would have to assay for two enzymes, take one away from the other; and so that's what we did on a whole series of blood samples sent down from the Edinburgh unit.

I **That's fascinating. Can I ask, was that actually the first work that you published, or had you already published some of the cholinesterase work?**

H We published the cholinesterase paper; I think we published that very soon after this. And then the… I think the publication on the… I think the publication on the dosage compensation came out after. [pause] The 'Genetical Studies on the New Variant of Serum Cholinesterase' came out in 1962, in Nature. So that was very soon after we got going. And then the red cell acid phosphatase polymorphism came out the next year, in 1963. The G6PD paper came out also in 1963. So we did the work at the beginning of that year but we were a little slow in getting it published, because … we had gone straight on with the human red cell acid phosphatase polymorphism.

And we started doing work on the, sorry, I've muddled things up a bit now: started telling you about the acid phosphatase. Let me back track: Harry spotted the Tsuboi & Hudson paper and came in with it one morning saying, "I've just found this paper" when he was at home, or going home on the train or something. And he'd seen these pH curves and it sort of reminded him of the qualitative analysis of the cholinesterase variants with the, different inhibitors; in the case of acid phosphatase we're looking for individuals with a different pH optimum, which might be genetically determined.

And so we looked for that; we could find nothing. And we did masses and masses of phosphatase assays together, Neill Spencer and I; and I said to him, "We could do this on gels. Why don't we do some gels on this?" And I said, "The only problem is, red cell acid phosphatase has a different substrate specificity so we can't use the diazo dye method; naphthyl phosphate substrate with a diazo dye to pick up phosphatase activity. So we messed about trying to work it out, in test tubes. We tried to work out an assay for red cell acid phosphatase, and decided that the only two substrates that were available were para nitro phenyl phosphate, and phenolphthalein phosphate. And, this is Neill's chemistry coming to the fore, both products are invisible, but both phenolphthalein and para nitro phenol, are acid-alkali indicators. So Neill had this brilliant idea of making the electrophoretic medium alkaline after we'd done the separation. So that's what we did. Put it in a box; it's quite simple. Put it in a sandwich box. And then we put sodium hydroxide in; dissolved the whole gel; it just disappeared!!. And then again, bright idea, a spot of 8-80 ammonia in the corner on a bit of filter paper; put the lid back on the box and there are these…[Pictures in the lab note book] that's what it looked like first of all; a little yellow band going anodally in a pH 8.6 gel. And this is with para nitro phenyl phosphate substrate at pH 6; that's the optimum, pH 6.

And that's November 1962. Two months later in January, we are observing one phenotype here with a strong band like this, weak band here; very strong band here, and quite a strong band here. And indeed that's what we call the common type; this is what we called the slow type; and then we also had a fast type, I'm not sure; I think we've got that here. We had the common type, which was those two; we had the slow type, which was called Naomi Byles, a medical student. And then this fast double type here. And that's Type A; that's Type C; that's Type B; and then this one is the common type but with a fuzzy band, which is in fact the fuzziness from this thing, which is BA; Type BA. And so those were by January of that year 1963… and so that's how that all came about really.

I **And so am I right that really, you already had several different enzyme systems that you were working on in parallel, really, and looking for variants?**

H Several. The Cholinesterase isozymes [published 1962] were closely related to the cholinesterase inhibition work, and were taken over by Mary Whittaker. Bette Robson was looking at placental alkaline phosphatase isozymes [published 1965] and a human serum phosphatase… The human red cell acid phosphatase isozyme polymorphism [published 1963] developed out of the qualitative analysis looking for a pH optimum difference; a few months later Neill Spencer and I discovered the Human Phosphoglucomutase isozyme polymorphisms and soon had some good results [published 1964].

Isoenzymes, or isozymes, were very much in the literature then, and had been at the time when I first started messing about with electrophoresis at the London Hospital, with the work of Clem Markert, on lactate dehydrogenases; Dick Tashian on red cell esterases; Also, Ron Davidson had done G6PD qualitative analysis by electrophoresis and discovered the Fast A+ type in negroes and the A- minus type also in negroes. Which of course, was an X linked polymorphism and therefore very different. We were also doing electrophoresis of Phosphogluconate dehydrogenase [published 1963] when Bob Fildes from the London Hospital joined us at Kings College and Bob soon discovered the AK isozyme polymorphism [published 1966].

Ron Davidson was visiting our lab at King's during this period so we were all kind of pooling our ideas together on what was possible; and in fact Ron did some lactate dehydrogenase isozyme work with Bob Fildes whilst he was with us on that trip… I think it was then… and discovered a rare variant of lactate dehydrogenase [published 1965] , which was extremely complex because of the tetrameric subunit structure of LDH.

Also we were gradually getting more technical help, because Neil and I didn't have any technical help at all at the beginning, and Neil was doing, you know, was teaching as well; and I was doing my chemical pathology at the London and stuff. Most of the lab technicians that we had at first were busy doing work for the practical classes, because there were a lot of practical classes in biochemistry for undergraduate medical students then..

I **Can I ask: did you, or did Harry, have contacts at all with Oliver Smithies? I'm thinking in terms of the development of the gel electrophoresis.**

H Yes. They were very, very good friends. They were extremely good friends, and that initial contact with Oliver and Harry and Bette, had taken place, of course, before my presence on the scene; and they were very busy doing starch gel electrophoresis for the haptoglobin and the transferrin polymorphisms, and trying different combinations… I mean, one of the ways in which this cholinesterase work, that I had stumbled into really, or had carried forward, was the fact that Harry and Bette had developed 2-dimensional electrophoresis where you could do paper electrophoresis in one direction, then take a cut off the paper and then put it into starch gel in the other direction, so you get charge separation in one dimension and then size separation in the other. And that was very significant in working out the relationship of this slow band in the C5 cholinesterase polymorphism from the C4 component. So yes, all of that was going on… and we used to do… I mean, before we got to this stage we went through every type of electrophoretic medium; we did it on paper; we did it in something called a Wiemer box, which was a way of doing Agar electrophoresis; then you could do it in a copolymer block, a synthetic copolymer block, an inert matrix which didn't give any filtration at all, and that was like a starch grain rather than a starch gel system. And then there was the starch gel itself, which I think, was eventually very simple but

initially when the starch had to be hydrolysed, partially hydrolysed, which is what Smithies did, it was extremely tricky.

Harry used to get starch from Smithies I think initially, so that they could do it. They were very good friends; yes. And other people, during this period, I mentioned Ron Davidson and others visiting the lab; there was quite a lot of folks coming and dropping by. And of course as well as the source of blood samples that I've mentioned from the Blood Transfusion Service through Cleghorn, like the Tristan da Cuhnans; we used to get material from Race and Sanger, especially when there were discrepancies in the blood groups which indicated perhaps some loss of material, chromosomal information, and whether we might be able to pick up unusual isozyme types, and occasionally it did happen later on, we would screen that material to see if there was evidence for apparent homozygosity for a, in an individual who was otherwise heterozygous. So that kind of early work in mapping and relating chromosomal composition to a phenotype went on.

I Can I ask what, as a person to work with, what kind of person did you find Harry Harris?

H Well, Harry was, he was always very enthusiastic. He was, however, there were some aspects of him that were unusual in the sense that he was very, he was very cautious in distributing information, until one was absolutely clear what its significance was and how it should be interpreted; or how it could be interpreted. And he would be, if we had people coming and it was something that we were just working on, he would be quite cautious about that. But then he would quite often, in the enthusiasm and the moment, then start chatting about it [laughs], which is fair enough, but it took a bit of getting used to. But he was always very affable to me. But he was also, he could occasionally decide that something wasn't quite right, and would therefore, he would stop talking to people for some reason or another. For example, he stopped talking to Mary Whittaker. Very close colleague and did the work on the cholinesterase. And although she'd moved from the London Hospital to Kings, for some reason the relationship broke down after she'd moved to Kings, and she was then in the lab upstairs and we didn't see much of her; and then she moved away eventually. I think she wanted the, I think she felt that she didn't have sufficient independence, and that was a feature of Harry. It didn't disturb me in any way because I felt that he was objective in his judgments, and we could argue between us the rights and wrongs of interpretation between us, and the next experiment to do. And if he thought it was better to do this experiment, then I would do that, and another one; whatever. So we didn't, actually, we never had any fallings out of that sort.

I Was he, at that point, a hands on person himself or did he very much have the ideas and left it to -?

H The only thing he claimed he would do better than anybody else was in this starch block separation technique, where it involved the use of a fat thumb along the line of the insert. But of course he was always smoking his pipe and there would always be ash all over this thing [laughs] so… and he had… of course we did have… he had a very good technical assistant called Nona; Nona Parry-Jones, who he met when he was at University College, when he worked with Datta Prakash. Of course Harry went with Warren to the London Hospital Medical School when Warren got the chair in biochemistry at the London. He was soon promoted to a readership, and in fact I can remember him being promoted to Reader when I was a student during that period, yes. So I must have known a bit more about Harry than I think, really, than I remember, as a student.

I At what point did the move across to the Galton and related building, happen?

H That happened in, I think, 1964, which is when this first report was produced. 64, 65. I guess it was 65. We actually moved up to University College, and we were aware that it was going to happen well before it happened, because Lionel Penrose [Galton Professor] indicated that he was going to retire, and he also indicated that he thought Harry would make a suitable successor. And I happened to meet the former director of the path lab at the London Hospital who was on the Board of Studies, and of course I knew him because I'd done the resident pathology job at the London; a chap called Harry May. I used to know him very well. And he said to me, he saw me on the train, I think; and he said, "We've just appointed Harry to the Chair at University College." And so I said, "Oh really?" I didn't tell anyone, of course. And that was in fact well, well before the news was announced. And so that was done in order that a new lab could be built, because the old premises at the Galton, they were on the main road and quite primitive in a laboratory sense. There was limited amount of lab work done. There was quite a nice cytogenetics lab that Penrose had set up with Joy Delhanty; and Jennifer Parrington was there as a PhD student at the time we moved. But the other labs at the old Galton were, just a series of rooms, and one or two big rooms were knocked into each other, but it was not the sort of lab we had at Kings College.... Our premises at Kings were very good. We had a modern research lab there with lots of benches and I think that had all been done possibly before Harry went to King's. , or because he was going there. Anyway, sorry, I'm changing; back tracking.

The premises at University College were temporary in the main quadrangle, and we stayed there for , I think, one or two years, probably two years, before Wolfson House, north of the Euston Road, was ready. And that was built from scratch. Nona Parry-Jones was involved, together with Harry, of course, but the architects and the designers and all the rest of it, were in communication; and that was state of the art with cold rooms. We'd discovered the importance of cold rooms in the early work on enzymes when, initially, if you look at the beginning of these books [See lab note books], the amount of activity we were getting; we were losing activity by not doing electrophoresis in the cold room, and we then started, you know, the cold room started breaking down and stuff like that. So we had built-in cold rooms next to the different labs, and also in the basement; very good facilities. We also had a facility for radiochemicals and also good facilities for cell culturing and so on. And then the top two floors were occupied by Grüneberg, Hans Grüneberg; animal genetics. And Grüneberg worked there for another, probably another 10, 15 years after that.

I And were Race and Sanger already, had they moved into the building at that point, or did that happen later?

H That happened after Grüneberg retired.

I But am I right in thinking that the MRC Human Biochemical Genetics Unit, and the sort of, the rest of the Galton, it was all planned that you should move into Wolfson House together?

H It was; yes. So we had the basement. There was a small section of the phonetics department on the ground floor, but we had the main part of the ground floor; big lecture theatre of course; and then we had big labs on the first floor; and then it went into a tower and we had the second and third floors above that. And then fourth and fifth floors were the animal genetics with Grüneberg. And then when Grüneberg retired, the MRC Blood Group Unit from the Lister Institute in London, came across; and Ann Mclaren's MRC Unit also came in. I can't remember the timing of that precisely.

I One thing that's always struck me is that there was a tremendous lot of collaborative

research between the different groupings in that building -

H There was.

I And it always struck me that that was a tremendously strong point. And I mean, well, how did you sort of, how did you see that coming about? Was it the personalities of the people being naturally collaborative, do you think, or was it helpful that everybody was in the same building?

H I think it was personalities in the sense that everybody got on very well; but it was also the fact that people could recognise the benefits associated with getting someone else involved to strengthen a certain area. And as I've illustrated in this very early work on these enzymes: there was a need for so many different things. For example, some of the enzymes that we started to look at were not accessible in blood, which was initially the main source; so we needed to collaborate to get other sources of material, and perhaps have cultured cells from individuals so that we could look at genes that were expressed in cultured cells that were not expressed in red cells or white cells. We could establish what their phenotype was by testing harvested cultured cells from those individuals. Or lymphoblastoid cell lines, which we also used for that same purpose. And we would always try to underpin what we were observing by our simple, relatively simple, separation techniques, by more sophisticated analysis and investigate properties such as molecular size, sub unit size, patterns of expression in different tissues, so that we developed very close links not only within our group but also outside. This had started off in the very early days with collaborations with the MRC unit up in Edinburgh for the cytogenetics and chromosomal abnormalities, the MRC blood group unit for the red blood cells, and the Tristan da Cunha blood samples coming from Tom Cleghorn, [N London Blood Transfusion Service] for example.

And then we started getting placentas, that's another aspect of our work that I haven't mentioned, the twin studies, starting initially with John Edwards who collected twins from all over Birmingham, and we characterised their zygosity. And of course the markers that we were developing were ideal markers to assist in determining the zygosity. And to be able to try to answer questions about the different types of placentation and how that related to the type of twin, whether it was a di- or mono-zygotic twin. And we then appointed Gerald Corney to be a member of the MRC Unit, and Gerald, not only did he have a specific interest in twins, he was also, became very important in collecting blood samples from families for our own studies. And he made contacts in the twin field and that led to the generation of sources of twin placentas from those parts of Africa where twinning rates are extremely high; so that we had twins from the Yoruba in Nigeria, and the Ibo and Kikuyu, I think, all with different rates of dizygous versus monozygous twins. And then we would do genetics by sib-pair analysis on systems that we couldn't get at otherwise in family studies. So that was a very important, those were very important types of collaboration.

And we also, in those days, of course we had no worries about, I suppose we should have done, but we had no worries about, we didn't know about AIDS, and we certainly, used to ship in dry ice, placentas from Nigeria by the score; little tubes. They used to be taken, popped into the freezer, and then into dry ice and would be collected and delivered to us from the airport. It was a huge operation. We used to get a lot of samples from South Africa; from Trefor Jenkins and George Nurse in Cape Town So, a lot of different sorts of African populations then to investigate; the peptidases, for example, which is another early enzyme polymorphisms; there was polymorphism among the black African population. So there was a lot of collaboration outside and a lot of collaboration inside the lab. And we became extremely intertwined… and that was certainly something which I felt was very important for the Unit, and certainly

something I tried to foster for the whole of my time there.

I To what extent did you yourself get involved in the gene mapping side? I always, and you can correct me if I'm wrong; I always had the feeling that Penrose and a group of people, probably including Peter Cook, were always fascinated by mapping. But that Harry Harris was much more interested in the biochemical variation rather than any of the actual map, yes? I mean, did you more or less go along with Harry with your particular interests?

H Yes; yes I did. I did. And that was because there was plenty to do [laughs]. There was lots of work, and I felt happy that we had Peter and also Sue Povey moving very firmly in that direction as well. Nevertheless, of course in the nitty gritty of some of the early assignments to chromosomes, using somatic cell hybrid techniques, we were all involved with that using electrophoretic techniques. That was just straightforward electrophoresis as opposed to the numerical LOD scores and linkage analysis that you've referred to. Yes, that, gene assignment and the ways in which we can get data about sub unit structure and so on by artificial hybridisation or somatic cell hybrids is the kind of biochemical side of things; but the linkage analysis, the LOD scores, were very much Peter Cook, Sue Povey and Bette Robson of course; Bette.

I At this point can I ask you a bit about Bette, because it doesn't really look as if she'll be well enough for me to see her.

H No, I think not; no.

I How did she first sort of come into this sort of orbit and area of work? Where did she start off things?

H She came to London and did a PhD on human birth weight. And I can't remember whether it was, Haldane was certainly around at the time, and, oh Penrose; she was Penrose's student. She must have been Penrose's student, and Haldane was involved. And Maynard Smith was around as well. And then, so Bette was, and of course she also became very friendly with Sylvia Lawler, on the blood grouping side. And yes, and gene mapping; and of course Cedric [Smith] as well. So that was that axis of things. And then she joined Harry at the London. She was funded by the MRC as 'external scientific staff' and had obviously had met Oliver Smithies, and got on well with Oliver, and learnt how to do the starch gel electrophoresis technique directly from the master. It was, I think, quite a difficult thing to get going to begin with. Partly because the starch wasn't available and you had to do this partial hydrolysis which Smithies invented, and then a company was set up where you could buy the starch directly, and it was no problem after that. But Bette was very early into the starch gel electrophoresis field, and worked with Harry. And of course they did a lot of human haptoglobin type and transferrin, and that stuff must have been done at the London.

Later, after we moved to King's College, she took on the responsibility for coordinating all of the family data that we did, so that as we gradually developed more genetic polymorphisms, to characterise our material; family material. Then we generated a group, and we called then 'The Group' who did nothing but starch gel electrophoresis for various enzyme markers in a big lab. [This was after we moved to Wolfson House, UCL] And they were run, Bette was in charge of that group, but they were run by a very good school leaver [Ann Harper] who had worked with us for a couple of years and picked up the techniques remarkably well. And of course in those days we used to get technicians straight from school, and they would come, perhaps still doing their evening classes; day release. And so all of that stuff became a routine, and also all the families that we did, their blood groups were also done. So we would send off bloods that we'd collected and bloods that the Blood Groupers had got, came in, and they all went

through this same process of scrutiny. And Bette coordinated all of that stuff, and looked for discrepancies as well as attempting to do LOD scores. And then -- Peter [Cook] joined the Unit and worked closely with Bette.

I One of the things that always stands out in my mind at the Galton was the kind of meticulous nature; that everything was checked incredibly thoroughly.

H Absolutely.

I Which I suppose was even more vital for the kind of work that was going on, than it is for other work.

Well, one thing I'd like to ask you is, when Harry Harris moved to America, this was quite a while before he was officially due to retire. Did that come as a bit of a shock to everybody or was it sort of half expected?

H I can't say it was expected but I had been aware for some time that Harry felt that he wasn't contributing as much; I think he felt that he wasn't as important to us, if you see what I mean, because we had a lot of… because of the cooperative nature of what we'd set up, we could get on with it, and get on with each other, and get on with other people as well. And I made, I think my first contacts with the forensic field were through Race and Sanger, who of course, knew a lot of people in the German blood grouping world; who used to go to forensic meetings. And I think as a result of that, Race that got me invited to some of those meetings, and then I used to see quite a lot of the forensic people, not only from Germany, but from Denmark, Switzerland and so on.

So you could see those things developing, and Harry was always, he always had a good time in the States; he knew a lot of people; was always asked to give talks; and was very well received. And people from the States would call in and see him and us; people like Barton Childs for example; very good friend. Kurt and Rochelle Hirschhorn, New York were also very good friends, People from Philadelphia; Bill Melman, a paediatrician, was at Philadelphia and very influential in Harry's move; so there was a lot of people… and of course Arno Motulsky and William Beutler on the West Coast at Duarte. And…. How can I forget her name? Blood grouper who got into -

I Phyllis McAlpine?

H Oh Phyllis. Phyllis was a PhD student. No, on the West -

I Eloise Giblett?

H Oh, Eloise, yes. Elo. How could I forget Elo's name? And Elo Giblett. And Nancy Simpson, in Kingston, Canada, Nancy did a lot on cholinesterase and she was a good friend as well. So you always felt that he had a good time in N America and there was always that possibility.

And I think…I think he could see this opportunity of going in a slightly different direction. The obvious direction to go was in the recombinant DNA direction because that was certainly on the boil and just becoming accessible to all; but he chose to go with monoclonal antibodies and using monoclonal antibodies as tools to unpick molecular relationships in proteins; and in particular the protein family of the alkaline phosphatases and in particular the placental alkaline phosphatase polymorphism . But of course he, after a few years, he did start doing some work with cloning and molecular techniques. But he wasn't, as we've already discussed, he wasn't, I don't think, ever technically a brilliant hands on person. He was very much an analyser of data; and a systematic analyser; and an absolutely unquenchable analyser. He would just go at it. If there's one thing Harry taught me would be to look at it from the top of

the page and the bottom of the page, and this side and that side; and then when he'd done that, turn it up and look at it from the other side, sort of thing. And would be very quick to appreciate the significance of practically derived results; very raw data. That was interesting. I found that very fascinating; that he could take raw data that you had slaved over and just look at it, and then make a few little smudges and squiggles and so on, and you know, how about this? Or come in with it the next day; and also explain it to people. I mean, he had a perspective which was different to my perspective because he had experience of, a lot of experience before I met him, in the field of renal inborn errors of metabolism, for example, and I think his writing was extremely good. He wrote very well.

I Yes, yes.

H His books on the, you know, on the rewriting of Garrod's Inborn Errors of Metabolism was excellent; Human Biochemical Genetics, Cambridge University Press, 1959 and also his first textbook [The Principles of Human Biochemical Genetics, published in 1970 by Elsevier] I thought was really superb. So that's why he went, I think, to Philadelphia, because he was feeling that he didn't have as much raw data in such a raw state, because people like me were processing it, and others in the MRC Unit, because we'd become more educated. And he knew that in the States he would have a good time. And his son was going to Cambridge; his wife had worked in government, I think, initially; she was a graduate and was very bright, and I think was looking for a different, for something different. So it was that combination of things.

I But he didn't really have awfully long before his health packed in, did he?

H He didn't. He was diagnosed with diabetes before I met him; and it was being talked about when I first went to Warren's department at the London Hospital Medical School in 1960. Warren told me Harry was working on something for someone at Kings College Hospital and he'd actually written a paper on diabetes, very early on. And then of course he discovers he's diabetic himself. And they treated him at Kings in the specialist unit there. And he used to get the most fearful hypoglycaemias. He was on soluble insulin all the time. And he would always have a biscuit on his person and there would be crumbs and messing and stuff all over the place. And his injection technique was extremely difficult, so it wasn't well controlled. And I think it was that rather labile type of diabetes that was hard to control. He was not a good candidate for long acting or mixed types of insulin, and many's the time I found him just before lunch in a hypo state and given him a biscuit or piece of chocolate or something. And that was certainly a feature. But he used to say that he was better, that he could work better, when he was a bit hypo.

I Hyper or hypo?

H Hypo. Yes. It's a bit like all of us really; when we're feeling a bit hungry and you feel, hmm, hunger for the knowledge as well as for the calories. So that's, yes.

I One thing I was wondering was, when the molecular, I don't like calling revolution, but it was fairly revolutionary; when molecular techniques came in, how did that impact on the work going on in what, by then, was really your unit after you'd become director.

H Yes. Well, we gradually embraced the molecular techniques; that's essentially what we did. And we used them to answer some of the questions that we couldn't answer, to give us greater clarity; and also perhaps confirm some of the things that we'd predicted.

So for example one enzyme that we studied at the molecular level was human phosphoglucomutase. We had predicted from our isozyme analysis, first started in

c.1964, there was a hot spot for recombination in the PGM1 locus. Using our own skeletal muscle expression libraries made by Yvonne [Yvonne Edwards] we cloned and sequenced PGM1 and David [David Whitehouse] and Yvonne showed the common phenotypes were attributable to a hot spot for recombination. Jim Neel [Ann Arbor] had also decided that PGM1 was an interesting topic, and we both published our papers in PNAS at the same time. Yvonne also used expression libraries to clone and sequence a muscle specific form of human carbonic anhydrase and several other significant human muscle specific genes.

We did the same thing, I mean Sue's group [Sue Povey] used molecular techniques to follow up long standing work in the Unit, that we had all been involved with for several years, on the human alpha 1- antitrypsin deficiency. Her group also used molecular techniques to examine the tuberous sclerosis gene where, of course, the precursor to that project was not enzyme electrophoresis per se, but a lot of family studies and gene mapping which placed TS on chromosome 9 and led to extensive collaborative work and indentification of the gene. Similarly Dallas [Dallas Swallow] did a lot of basic biochemistry and genetics on lactose intolerance families and followed that up in collaborative studies on the lactase at the molecular level with colleagues in France and many other centres. Dallas Swallow also did fundamental studies on the biochemical genetics of human mucins and their highly repetitive structures and this too moved steadily on to further studies in the Unit by molecular techniques.

Ben [Ben Carritt] another member of the Unit began to use recombinant techniques to carry out fine physical mapping of part of the short arm of chromosome 1.

I too had enormous fun working with Phil Johnson on denaturing gradient gel electrophoresis and the ABO blood groups. This was an area of technical work that I greatly enjoyed; and we were able to subdivide the A and the B groups, as I recall.

Our overall strategy was to combine the old approaches [serology, protein analysis] with the new [DNA,RNA].

I **There's one area which has always seemed to be very different from most of your other interests and that's your interest in genetic factors in facial features .**

H Yes. That was a very late, I wouldn't say that was a late interest, but it was a very late introduction to the Units research programme in 1995, and I thought it was a very long shot and something that I could do, or have a very close hand in, during the last 5 years before I retired. That's why I put that programme in. However, the scanning system wasn't as sophisticated as I thought it was, and the programmes for analysing the facial features were not as sophisticated or sensitive as I thought they were going to be, and it was frustratingly difficult to access the information. We would scan faces and we had quite a nice setup, because we were able to get a place in the new Wellcome Wing of the Science Museum. And half terms and end of term time, like coming up now, at the time of this interview, we would have dozens of people walking into the lab in Wellcome Wing as families; and of course they tended to visit in family groups to look at the exhibits. But the frustration was, although we could see some features by scanning contours, we couldn't interrogate them in the ways that I wanted to; and it took forever to write programmes to produce the sorts of things that I had in mind.

I **Has it changed much since, do you think? I occasionally see one or two things about it, but I haven't seen very much recently.**

H Nope; no. The only thing we could say with any degree of confidence, which I think was fairly well established, is the cleft chin has a very strong genetic impact or element; and there's a couple of other features in the brow regions. Again, not surprisingly, but too difficult; it was [sighs]… It's a little bit like looking at this acid phosphatase, going back

to the beginning, and just using one quantitative technique; and what we needed was more qualitative analysis in the geometry of the shapes, and to be able to classify in that sense. And the boundaries were just too blurred; and we really didn't get anywhere apart from those three features. And I haven't seen anything significant since.

I **If you look back over the years, I've been asking everybody this question: which piece of work do you feel most proud of, or most attached to, of the many areas you've covered? Is there one that stands out?**

H [long pause] It's very difficult to choose because I mean clearly the enzyme polymorphism work as a whole, I feel, was the most significant work, and I found that the most satisfying and the most interesting. Each individual enzyme within that range of enzyme or isozyme systems had their own particular interest. And also, coming out of that, I did enjoy very much the analysis of sub unit structure which pulled everything together, and the distribution of monomeric versus multimeric; and then the diversity of the multimeric, and then the diversity yet again associated with multiple loci with interactions between loci in some cases, but not in others. So clarifying that, I suppose, is a more unifying theme than just simply to say, "The isozyme systems as a whole were the most satisfying." So I think putting that together, and also looking at the patterns of variability and discovering, as one might predict, that the monomeric proteins are, in general, more variable than the multimeric; and the constraints are greater on the multimeric than you would expect.

And then again there is other pleasure associated with other people's work; in discovering that acid phosphatase, for example, which was always a puzzling polymorphism, right from the very beginning [I submitted my MD thesis on red cell acid phosphatase in 1966] . It was a puzzle then as to why there appeared to be more than one component determined by a single allele in this monomeric protein. They were not multimers, It turned out that the differences are generated by splicing; they're alternative splicing of gene products. It was very hard to think of this mechanism before we had molecular techniques. As soon as I saw that paper, and this was work done by very good friends of mine, a Danish friend [Joergen Dissing] and an American [George Sensabaugh], who worked together on this; and I saw that it explained all of those kind of worries when I was putting together my thesis for the Cambridge MD and the various suggestions that I'd put forward about multimers or conformational isomers, which didn't quite fit. And that was way back in 1964/5, I think I wrote the thesis, and to get the proof of it all those years later. And the fact that people were working on it and still finding it interesting, was very rewarding.

I **The other thing I've been asking everybody is there one particular person that stands out as having been a special influence on the development of your work and career?**

H I think I would say that Harry Harris has been the most influential person because he certainly saw very early on that we could work together, and that we could generate, we could generate quite a lot of exciting results that we could think about, and perhaps resolve; perhaps not.

I **Now are there any other things, there are lots of things we could go over, but are there any things that you feel you'd like to sort of say or put on record, that I haven't really covered at all?**

H I think we've talked about most things. You introduced the topic of collaboration; the fact that we collaborated a lot within the Unit and we collaborated a great deal outside; and that was another cause of very great pleasure, and was very productive, both for us and I hope for people who collaborated with us. And it provided a level of openness

that was very rewarding, really. And frankness: the opportunity to be frank; if you have been part of something you can speak your mind, whereas if you've only been looking at it when it's, you know, you're coming into it rather late on, you can't be quite so frank. In fact, you had a responsibility to look at it early and sort out problems early on. That's again, one of the purposes of that kind of collaboration, that you would start and tackle things head on before they got into a mess.

I **Well, many thanks. I'm going to turn the machine off now, and then we can carry on chatting afterwards. Thanks very much indeed.**

H Pleasure.