

An Unexpected Journey: From Experimentalist to the Human Developmental Biology Resource



Susan Lindsay

Abstract The Human Developmental Biology Resource has enabled human development research and the understanding of congenital disease for over 20 years. I was involved in its inception in 1999 and ultimately became the Resource's co-Director for nearly 15 years. How did my scientific journey lead me to this position? I started my career as a research scientist in 1980, following the traditional pattern of Ph.D. then post-doctoral positions, initially studying the human X chromosome and searching for X-linked disease genes. By the mid-1990s, characterising and understanding gene expression patterns during human development was an important part of my work, partly because my searches for disease genes weren't fruitful and partly because of my interest in embryology. At the time, studying human embryonic tissues was an unusual thing to do: it was expected that animal models would provide the important answers. My colleagues and I, however, thought that investigating human development directly could provide key insights into human congenital disease. The difficulty was that human embryonic tissues required for this research are intrinsically challenging to obtain: raising ethical, practical and experimental issues. Thus, as my career progressed, I became more involved in establishing the human tissue bank which in 1999 became the Human Developmental Biology Resource (www.hdb.r.org): a significant international resource that has been expanding and innovating for more than twenty years. Personal circumstances and funding possibilities contributed to the decisions leading me to this fundamental change in role: from making scientific discoveries to enabling researchers to carry out ground-breaking work which otherwise would have been difficult or impossible for them. Now at the end of my career, I see very clearly how valuable and how vital a part of scientific endeavour are service organisations which facilitate research by providing much needed resources and I'm proud of my contributions to HDBR.

S. Lindsay (✉)
Newcastle University, Newcastle Upon Tyne NE1 7RU, UK
e-mail: susan.lindsay@newcastle.ac.uk

1 Motivations: How I Developed an Interest in Science

Biology was my favourite subject at school and this enthusiasm survived even the teacher who, during the lessons on reproduction, scurried from side to side at the front of the classroom crying “no questions, no questions”. The teacher was male, and it was an all-girls school! My next biology teacher (Miss Stevenson) was excellent, answering lots of questions and sparking my interest in developmental biology and genetics, subjects which I took forward to university in Glasgow in 1976. Scottish undergraduate degrees have 4 years of study, which gives scope to try different subjects in the first and second years building towards an honours course in the third and fourth years. Although I’d studied genetics in my second year, the same year as introns were first reported, I chose zoology because developmental biology was a strong element in a wide-ranging zoology honours course.

I wanted to undertake a Ph.D., but I always had a whole range of scientific interests rather than one burning question. I also had a romanticised (i.e. highly unrealistic!) idea of what science is and what being a scientist meant: it was people who were “lone geniuses” working away in isolation and having a “eureka” moment or moments. Despite being uncertain about whether I could become a scientist, I decided to look for Ph.D. places and was accepted by Marilyn Monk at the UK Medical Research Council (MRC) Mammalian Development Unit at University College London (UCL). As often happens, my Ph.D. subject area changed: from investigating X inactivation in embryonic mouse germ cells to studying differences between human active and inactive X chromosomes, trying to find molecular mechanisms involved in X inactivation. This was fortunate as the technologies I needed to learn were at the cutting edge of molecular genetics, a fast-moving new field, and X inactivation is intrinsically interesting: why does one of the two X chromosomes in female mammals get switched off?; how is this one chromosome chosen and is it the same X in every cell?; how does it actually happen?

As I moved from Ph.D. to post-doctoral positions although I could construct a connecting theme, there was no one specific question or area that I was driven to pursue. Partly because of this and partly because of funding, my motivation was more in the day-to-day and the question or questions I was addressing in each project. I mostly enjoyed working in the laboratory although it was discouraging when experiments failed and it was unclear why, often leading to many rounds of troubleshooting! However, I also found excitement and even wonder during my experiments, such as the first time I precipitated human DNA and thought about the myriad of possibilities, opportunities and questions left to answer in this amazing gloopy substance in the test tube. I’m sure many scientists have had this moment.

2 Work Done: My Personal Scientific Approach

(1) The shift from experimentalist to resource director

I was fortunate to work with excellent scientists at many points in my career. They were also very different from each other which gave me several models of what a scientist is and highlighted many of the elements of what makes up “Science”.

First steps towards being a research scientist

My Ph.D. supervisor, Marilyn Monk, was a highly individualistic scientist who was both meticulous and creative. She had a very particular way of approaching her research including a leap of imagination to place herself “in the cell or nucleus” aiming to see different perspectives. She was a mouse embryologist investigating the formation of the primary germ layers; the role of X inactivation in these processes and using the choice of inactive X as a marker for differentiation. My project was to look for differences between human active and inactive X chromosomes at the DNA level and, as part of this, to bring molecular genetic techniques from the National Institute for Medical Research (NIMR), Mill Hill to Marilyn’s lab at the MRC Mammalian Development Unit, UCL. At that time (the early 1980’s) I was learning very new technologies: using restriction enzymes (some of which I had to prepare from scratch!), Southern Blotting and DNA hybridisations.

One of the things I learnt from Marilyn was the importance of controls and that thinking about them helps you to understand whether the experiment you’re doing is the experiment you intend to do! She had a variety of horror stories but one in particular stays with me to this day. On a visit she made to a laboratory where a Ph.D. student was explaining his project to her, she asked what happened when the petri dishes of different bacterial strains were placed under the UV lamp in a different order. The student realised that his data did not show UV susceptibility of different bacterial strains but rather the different strengths of UV output across the machine.

I studied differences in DNA methylation between active and inactive human X chromosomes. The picture was confusing and didn’t fit with the straightforward hypothesis that increased global methylation was involved in gene or chromosomal inactivation. Over time it emerged that DNA methylation was one of the important mechanisms involved in X inactivation but that it was specific changes in specific regions that were critical. The DNA methylation field and the variability of results and shifting response to them showed me that often a new mechanism is hailed as *the* answer to a particular question, then exceptions are found and the mechanism is deemed not to be the answer at all. As evidence accumulates, a more nuanced understanding is reached of the complexity of the problem that the question is addressing.

First post-doc: still fascinated with DNA methylation

My first post-doctoral position was with Adrian Bird at the MRC Mammalian Genome Unit in Edinburgh. It was an exciting time to join Adrian’s group as they

had just identified “CpG islands”, a new and, as they discovered later, very common kind of promoter (Illingsworth and Bird 2009).

Paradoxically, although CpG dinucleotides are less common than expected from nucleotide composition, there are specific regions in vertebrate DNA where they are clustered and abundant, the CpG islands, and cytosine DNA methylation is key to both phenomena. In the mid 1980s, before the human genome sequence was published, finding genes in human DNA was difficult and laborious. The discovery that CpG islands were promoter sequences potentially gave a whole new way of identifying genes as some restriction enzymes could be used to find the clusters unmethylated CpG dinucleotides.

My project was to see whether identifying CpG islands in cloned DNA (where all DNA methylation is removed) was an effective way of finding gene sequences on the human X chromosome. Satisfyingly, it was in three out of the four clones identified (Lindsay and Bird 1987).

Adrian Bird embodied my preconception of a scientist, highly intelligent and focussed on his research but not, I soon realised, working in isolation. His team, including excellent technicians and research officers, as well as students and post-docs, made important contributions to the development of his work.

Second post-doc: from MRC to university

I worked in MRC units in both my Ph.D. and first post-doctoral position. At that time (mid 1980s), the MRC funded the research in units so individual group leaders generally did not seek external funding. This was beginning to change and for my second post-doc, Shomi Bhattacharya introduced me to grant writing which from then on was an integral part of my life. Shomi was based in Edinburgh at the MRC Human Genetics Unit and also at Newcastle University. When he moved to be fully in Newcastle, I went with him. While in Edinburgh, Shomi and his colleague Alan Wright were one of the first groups to use molecular tools to identify a chromosomal region where a disease gene was located (Bhattacharya et al. 1984). The disease was an eye disorder, X-linked retinitis pigmentosa, and positioning the locus along the chromosome, although a very major step, was just the start of the work. I joined the group as they were searching for new markers to refine the position of the gene and beginning the search for the gene itself. This was a very different type of project for me, particularly because family studies (following the inheritance of a disorder in relation to different alleles of a marker or markers) involved the human element of meeting family members who made the crucial contribution of genetic material (usually from blood) underpinning the entire project. It was also my first experience of research where inputs were necessary from people with very different expertise, including genealogists, clinical geneticists, genetic counsellors and bench scientists as well as close collaboration between staff in the NHS (UK National Health Service) and in the university. Shomi set up one of the early NHS molecular diagnostic laboratories which ran alongside his research group, and this proved a very fruitful model both for research and for translating research results into clinical tools.

A change of direction

In the early 1990s Shomi took up a professorship in London and, for family reasons, this time I didn't go with him. Tom Strachan then became Professor of Human Molecular Genetics in Newcastle and I continued with family studies and projects aimed at identifying disease genes involved in X-linked disorders. Although Tom's group and others in Newcastle were very successful at identifying disease genes for a range of disorders, my projects did not reach this goal. This was very disappointing but one of the approaches for screening possible candidates led to what was to become my main focus for the remainder of my career. Many genetic disorders have their origins during embryonic or foetal development and it was expected that the genes responsible should be active at relevant times and in relevant tissues during development. Tom and the head of Clinical Genetics, John Burn, set out the case for human embryo research (Burn and Strachan 1995) and they, along with Stephen Robson, an excellent, research-active obstetrician, and I collaborated to gain funding from Wellcome for a pilot project to collect human embryonic tissues for gene expression studies. The project started in 1996 and from the outset, we wanted to study mRNA expression. This meant that the tissues had to be collected quickly after the termination of pregnancy and processed with great care to preserve as much high-quality mRNA as possible. The success of our methods was clear from the reproducible and specific data gathered for several studies: for example of *HLXB9*, a major locus for Currarino Triad (Ross et al. 1998) and *SHOX*, which underlies some aspects of Turner Syndrome (Clement-Jones et al. 2000).

Genesis of the Human Developmental Biology Resource (HDBR)

Also in the early 1990s, a group at the Institute of Child Health (ICH), London, had a pilot project funded by the MRC to collect and carry out gene expression studies on human embryonic and foetal tissues. They, like us, recognised the importance of not wasting any of the tissues collected and so both groups provided tissues to other researchers. The complexities of creating our collections within a robust ethical framework and the increasing demand we foresaw for the tissues, led to successful applications for joint funding from the MRC and Wellcome, resulting in HDBR being established in 1999 (www.hdbr.org; Lindsay and Copp 2005). HDBR has been continuously funded by the MRC and Wellcome for more than twenty-three years. In London it has been led throughout by Andrew Copp and in Newcastle, firstly by Tom Strachan and then myself, when I took over in 2004 until I retired in 2018.

In the early years, the prevailing orthodoxy was that studying animal models (e.g. *Drosophila*, chick, mouse) would tell us everything that was important about human. Our work, for example on *SHOX* a gene that doesn't exist in mouse and others (e.g. Fougousse et al. 2000) showed that this wasn't always the case. Furthermore, there was a very interesting change as the field moved from identifying genes underlying genetic disorders, to studying their function and to trying to find therapies. It became crucial to know precisely what happens in human (e.g. timing and site of expression and specific gene involved). As time went on, the importance of studying human development directly became much more widely accepted: for projects aimed at

understanding and developing therapies for specific diseases and, more generally, for understanding human development, particularly brain development, at a molecular genetic level.

(2) HDBR: major elements

Tissue collection, ethics and guidelines

Throughout my involvement with HDBR, first as co-investigator in Newcastle and then as HDBR Newcastle Director from 2004, the ethics of collecting and using the tissues were of paramount importance. Cultural sensitivities, legal requirements and practical considerations all make collecting human embryonic and foetal tissues difficult in many places and impossible in some. In the UK, the 1989 Polkinghorne Report set out guidelines for the use of human embryonic and foetal tissues in research based on the presumption that, if possible, using these tissues for research was beneficial. The main principles it identified were:

- the decision to terminate the pregnancy must be before and separate to requesting consent to donate the tissues for research;
- there should be no discussion of the specific research the tissue would be used for i.e. consent would be generic;
- the tissue should be anonymous and held by an intermediary body, separating the research team from the medical team caring for the donor.

From the beginning, HDBR has followed the Polkinghorne Guidelines, acting as an intermediary body between researchers and the medical staff caring for the donors. Consent was obtained by research midwives or nurses and in the early days, in line with Polkinghorne, gave very little information about the types of research that might be carried out. Following several scandals relating to human tissue and a general change in the UK public attitude to consent, the Human Tissue Act was passed in 2004, followed by the setting up the UK Human Tissue Authority (HTA; <https://www.hta.gov.uk/>) in 2006. The HTA regulates, licenses, and inspects a wide variety of activities concerning human tissues and produces codes of practice (e.g. code A—consent, code E—research) for guidance. The other crucial regulatory bodies are the Research Ethics Committees (RECs; <https://www.hra.nhs.uk/about-us/committees-and-services/res-and-recs/research-ethics-service/>) which scrutinise proposals for human research. From its inception HDBR has also had a Steering Group which has independent scientists as Chair and co-Chair and includes a lay person and, in later years, a legal expert with an interest in tissue banks.

Consent was a major issue and, as I outlined above, ideas of what was appropriate changed radically over the nearly 20 years I was involved with HDBR: from a position where providing essentially no information about the research was appropriate to a position where to be meaningful, donors had to be given some information about the research in order to make a decision. Generic consent was allowed but you had to indicate the types of research that might be carried out and specifically address any areas that might be sensitive or where donating tissue might have future consequences. One example of the latter, which was explicitly addressed in more recent

HTA and REC guidelines, was sequencing of embryonic and foetal DNA and RNA. Even though the tissues we collected were anonymous (HDBR had no identifying details about the women who donated them), as computing power increased and the programmes for searching and comparing sequences became more sophisticated, there was the theoretical possibility that the sequences from the foetal tissues and the woman could be linked: for example if the woman had donated a sample of her own DNA for sequencing to a private database (e.g. one of the ancestry-searching companies), along with her personal details and the security of that database was compromised. We altered the patient information leaflet and consent form to take account of this concern and others over time, but it was the skilled research midwife and nurse team who took the consents and answered questions who really helped women to understand clearly what everything meant. We were fortunate in HDBR Newcastle to have a senior research midwife, Allison Farnworth, involved over many years and her input to planning and governance meetings helped me, and my team understand and appreciate the reasons why women wanted to donate their tissues; the most common one given was so that some benefit might come from a difficult situation.

The importance of defining terms

At the beginning, HDBR Newcastle collected only embryonic tissues, from approximately three until eight weeks of development (Bullen et al. 1998). The embryonic period in human is divided into 23 Carnegie stages (CS) based on features that are present (e.g. during limb, eye, ear development), embryo size and age (O’Rahilly and Muller 1987). This is a critical period when all major organ systems form. Developmental age starts with the fertilised oocyte and is described as either post-conception or post-implantation. Something that can cause confusion is that obstetricians use the term gestational age which begins approximately two weeks earlier, at the time of the last menstrual period. There is further confusion if researchers use gestational age but mean developmental age! Another confusion arose with the new field of human embryonic stem cell (hESC) research. The term embryo was then often restricted to only the time when hESC could be derived i.e. 0–14 days of development and the period after that was called foetal development. We used developmental age with the embryonic period being 0–8 weeks. In the foetal stages that follow, there is significant growth and further differentiation of all systems. As for many aspects of science (and life!) it is always important to define your terms.

Keeping track as HDBR expanded

In the early days, HDBR Newcastle embedded most of the tissues it collected and provided tissues as sections on glass slides. This meant that, depending on its size, a single tissue could generate hundreds or even thousands of glass slides. It was clear that tracking all these slides would be very important and not an easy thing to do. We started with an access database for Newcastle samples and finally had a custom database built because, by that time, the details of tissues from both London and Newcastle were held jointly in the database, which was updated in real-time with information on the tissues (how, where and when they were collected, developmental

stage), how they were processed (e.g. wax embedded, frozen, DNA and/or RNA prepared), which project individual slides, tissues or other material were assigned to and when slides were returned. As you can imagine, this is a very large database as many tissues have been collected and processed into thousands of items and HDBR has contributed to more than 750 projects (Gerrelli et al. 2015).

A resource that provides services is very different from a research group. Shortly after I became HDBR Newcastle Director, I sought help and advice from Ann Curtis who headed the Molecular Diagnostic Service in Newcastle. She kindly showed me the rather daunting folders of standard operating procedures, risk assessments and policies for every aspect of the service. I hadn't thought about formalising our day-to-day activities in such detail but began to do so, with the help of my colleagues. It was an eye-opening process! Of course, we had experimental protocols but not, for example, procedures for recording version number or standard dates for review. We also didn't have any knowledge of how the services the university provided us with (e.g. computing, electricity supply) were risk assessed, backed-up or supported. Fortunately, by the time that information was required by the HTA, we were part of Newcastle Biobanks (<https://www.ncl.ac.uk/biobanks/>), which covered all the tissue collections in the Faculty of Medical Sciences and had, amongst other staff, a quality assurance manager who had expertise in many aspects covered by the HTA licence. So all we had to do was provide the information we had on HDBR's workings!

Collaboration is all: interactions between the HDBR sites and with researchers

At first the great majority of the material sent from HDBR Newcastle was to groups outside Newcastle. HDBR London, on the other hand, was initially set-up for research groups based in London to collect tissues directly from the HDBR laboratory and take them back to their own laboratories for processing. So at the start, probably because of the size of the "interested research groups" pool in Newcastle and London, the two HDBR sites had very different set-ups. Expertise grew on both sites and there were exchanges of ideas, protocols, and policies. By the time we had the joint custom-made database, both sites had extended their activities considerably and were operating jointly in much more standardised ways (Gerrelli et al. 2015).

Our interactions with many research groups went well beyond simply providing material (tissues/slides/cells/DNA/RNA/protein). Our knowledge of human development helped with planning which stages were appropriate to include for the specific questions the researcher was investigating. Some researchers visited the laboratories to show us techniques which we then used to tailor the material we sent for their experiments. We set up an in-situ service which carried out gene expression studies which was advantageous for research groups whose expertise was in other fields but who needed the gene expression data to add to their evidence, often for a publication. For us it meant we had the opportunity to capture images of all the data. As I will discuss in the next section, I felt very strongly that it was important to make publicly available all the data that we could.

An important long-term collaboration for me personally and for HDBR Newcastle was with Gavin Clowry, a researcher in Newcastle whose interest in cerebral palsy led him to study gene expression in the developing human brain, particularly the

cortex. HDBR Newcastle originally didn't collect foetal stages but began to do so in response to requests from researchers. We then had to gain the anatomical expertise for these stages as we had earlier for embryonic stages and Gavin worked closely with us to share his knowledge of the developing foetal brain. I collaborated with him on several of his studies of cortex development (Clowry et al. 2018) over a time when new technologies and wider access to human developmental tissues (with a major contribution from HDBR) enabled significant gains in understanding to be made by many groups both of key developmental processes and of the roles of specific genes in a wide range of disorders of the cortex (Molnar et al. 2019).

Nothing stays the same: new technologies and innovations

In the last decade or so advances in sequencing technologies have reduced the cost and increased the speed of sequencing both DNA and RNA, making large-scale projects feasible. I was keen that HDBR kept updating its services. One example was a collaboration to produce systematic RNA sequence data from different brain regions from approximately 4 to 17 post conception weeks (PCW). The datasets were deposited in ArrayExpress [now ArrayExpress in Biostudies] and the details and links are available from the HDBR website (<https://www.hdbbr.org/expression> (Lindsay et al. 2016)).

The huge changes in the capacity for generating and analysing very large quantities of data and the increasing number of significant results showing human prenatal development as a critical time when many genetic diseases arise, have led funding bodies to support major research programmes on human development. In the UK, the MRC and Wellcome have been very forward-thinking and provide funding to large-scale programmes such as the Human Development Cell Atlas (<https://www.humancellatlas.org/dca/>) and The Human Developmental Biology Initiative (<https://wellcome.org/press-release/wellcome-funded-initiative-unlock-secrets-human-development>). HDBR is an integral part of both programmes, providing national and international researchers with material (e.g. Behjati et al. 2018).

How to capture, analyse and make image data public

DNA and RNA sequence data can be made public in relatively straightforward ways and there are a number of accepted repositories e.g. European Bioinformatics Institute (<https://www.ebi.ac.uk/>). For image data, such as those generated in many projects HDBR contributed to, it is more difficult as the precise location of the section or cell within the tissue is often important and not easy to specify consistently. This is even more difficult for developmental stages where there are large changes in shape, size and cell composition of organs over time.

I found the solution for HDBR in a collaboration with Richard Baldock and Duncan Davidson who co-headed the Edinburgh Mouse Atlas team (<https://www.emouseatlas.org/emap/home.html> [archive only now]) and had developed a gene expression database (EMAGE) and a suite of software for analysing and comparing gene expression patterns, including for mapping them to 3-dimensional (3D) models of each stage of development (Christiansen et al. 2006). James Sharpe, a member of their team, developed a novel method for generating 3D models of mouse embryos

(optical projection tomography, OPT; Sharpe et al. 2002). We were able to generate 3D OPT models from all stages from Carnegie Stage (CS)12 to CS23 (approximately 4-8PCW) which had a much higher resolution than any of the models then available (<https://hdbratlas.org/3Dmodels.html>).

My 3D spatial awareness is not strong and mapping data to 3D models helped greatly with visualising and understanding results generated in different experiments, particularly when we identified and “painted” anatomical structures in the models, initially for the developing brain in collaboration with Luis Puellas and his team in Murcia and later for other organ systems (<https://hdbratlas.org/organ-systems.html>).

The importance of an excellent team

Over the years I was supported by an excellent team in Newcastle. In particular Steve Ligo, HDBR Newcastle’s Resource Manager, was key to the success of HDBR from an early stage. Steve was involved in, and led many of, the changes, expansions and innovations. Amongst numerous other talents, his people skills help foster excellent working relations with HDBR London and the researchers around the world who use HDBR, as well as encourage and support the scientists and students who have been part of the Newcastle team over the years.

3 Science Today and Tomorrow

There are many different tissue collections and over the last fifteen years there has been a drive towards optimising and harmonising them as well as making it easier for researchers to find the samples they need for their research. In Europe in 2014, this had the logical outcome of establishing the EU Biobanking and BioMolecular Resources Research Infrastructure—European Research Infrastructure Consortium (<https://www.bbMRI-eric.eu/>). BBMRI-ERIC’s Directory enables researchers to find a biobank with tissue samples they’re interested in, for instance from patients with a particular disease. It also provides tools and expertise to help biobanks e.g. with ethical, legal and social issues. I think it’s likely that this drive will intensify, particularly alongside the trend in many countries to regulate human tissue banks (e.g. by the Human Tissue Authority in the UK).

For HDBR and other biobanks collecting human embryonic and foetal tissue, the major worry is the availability of tissues in the long-term. They are vulnerable to changes in legislation surrounding termination of pregnancy (such as has happened in the USA recently) as well as changes in clinical practice. Fortunately, new technologies, such as spatial transcriptomics (Williams et al. 2022) which HDBR now provides as a service, are enabling large quantities of data to be gathered from small samples, helping to make the best use possible where available tissues are limited. The development of human stem cells and methods to differentiate them into specific tissues have provided powerful tools for understanding disease causation and testing possible therapies. The gold standard is to validate stem cell differentiation against

what happens during human development (e.g. Collin et al 2019) and I can see tissues being requested for such studies for some time to come.

Our two databases are very important to HDBR. The tissue collection and project database I described above, although large, is a standard relational database containing text and numerical data. The gene expression database, on the other hand, is image-based and presents a much more difficult problem. It is a huge and expensive task to develop and maintain image databases where it is possible to search and cross-compare the data within them. We were fortunate to be funded by US NIH from 2002–2009 for the initial development of the human gene expression database and generation of 3D models and following that, MRC and Wellcome supported the continued mapping of gene expression data as part of HDBR. When Richard Baldock retired, the EMAGE database stopped being updated as did our database. All the images are now available on the Image Data Resource (<http://idr.openmicroscopy.org/>) which is an excellent repository but it is not set up for cross-analysis of data in 3D models. The Allen Brain Atlas has developed a Brain Explorer that allows these comparisons for their adult mouse brain gene expression data (<https://mouse.brain-map.org/static/brainexplorer>), however it is not yet available for their developing human data. I hope that technologies will evolve that make storing image data; identifying anatomical domains in 3D models and analysing multiple gene expression patterns within them much easier and more affordable. Funding for image-based gene expression databases is difficult to obtain but if the technologies genuinely allowed searching and comparisons in 3D space, with related anatomical domains, then I think that the substantial aid they provide to understanding complex spatial relationships would be a very strong argument for the significant funding that is needed.

4 Advice to the New Generation of Scientists

‘Do what you’re interested in’ was my starting point but the carefully crafted CVs of Ph.D. student and post-doctoral applicants that I’ve seen suggest that much more thought is needed nowadays about where (in subject and place) you’re aiming as well as knowledge of what might be needed (skills, additional qualifications etc.) to get you there. Fortunately, I also think there’s much more help and information available now, from university careers offices to the websites of institutions and research groups you might be interested in. The latter often have “meet the team” short biographies of people at all different stages of their career which can help you to think about what might be needed.

It’s likely that your scientific career will change over time so you will need to be prepared to train and retrain and continue seeking help and advice (a hopefully enjoyable experience!). I realised when I became a supervisor that it was very much easier to supervise someone who came to ask for help and said when they didn’t understand or something wasn’t working. In retrospect I think I must have been difficult at times to supervise as I often felt that I should tackle things by myself and, I’m sure, there was much less discussion than I certainly would have benefited

from. So, if you can, recognise what you find difficult, seek help, and use all the resources available to you to overcome these difficulties. Equally, testing your ideas and enthusing or being enthused by your peers and colleagues adds greatly to enjoying your work.

Don't be disappointed when things don't work out as you expect: this is often a pointer to the need to rethink your experiment and make some changes. At times it may also suggest that there is a need to change some aspect of your job or career aspirations. There are many ways in which failing at something is helpful and can have positive outcomes. I realise this is easy advice to give and I certainly felt failures keenly and often took them personally: it took some time to realise that this wasn't a useful way to think of them. It's hard, for example, not to be disappointed when grants are rejected. Some grant referees and grant bodies, however, are extremely good at helping you to understand how to make improvements. Grant-writing has also become much more professional and there are now many more resources to help you improve your techniques. Universities (like other organisations) are helping their staff to improve and strengthen their grants, recognising that this should improve the hit rate for gaining grants which is in their interests too. Being part of grant reviewing processes is very helpful in strengthening your craft and, similarly, reviewing papers improves your skills as a paper writer.

There are many ways of being a scientist and many kinds of contribution that scientists can make. It's helpful to be aware that your career is for the long term and will change over time, which can be a good thing. At different phases in your career the skills needed for your work will change, often in unexpected ways, so keep learning new skills. Working and collaborating with people from different disciplines also keeps work interesting and challenging. A lot of my work was with computer scientists which gave me new perspectives on many problems. Learning new technical terms wasn't so difficult but recognising when we were using the same term and meaning very different things was tricky.

Nowadays there are a multiplicity of careers for scientists: one person's ideas often need many people to help refine, test, and implement. As I found out, this includes scientists generating and running the gamut of resources that modern multidisciplinary science demands.

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Susan Lindsay obtained a first class honours zoology degree from Glasgow University (1980) and a Ph.D. from University College, London (1984). After a short time in a Los Angeles laboratory, she was a post-doctoral scientist at the MRC Mammalian Genome Unit and the MRC Human Genetics Unit in Edinburgh, before moving to Newcastle University (1990) where she was lecturer, senior lecturer and finally Professor of Human Developmental Genetics from 2006 until retirement in 2018. Research interests were in the molecular genetics and 3D modelling of the developing human brain and in leading a unique UK resource of human developmental tissues.