Do we all feel we succeed despite the system?

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Endocrine-Related Cancer (2012) 19 P9–P12

My current role is Professor of Endocrinology at the University of Manchester in the UK. Having held major jobs in the University as Dean for Graduate Education and for Business Development, I am now very fortunate to have a role where I split my time between teaching medical students, doing several management tasks and running a very lively research group. We have two areas of scientific interest with potential diagnostic implications: one group works on hormone-secreting tumours and the second team looks at the stress axis and regulation of food intake and glucose homeostasis with relevance to metabolic syndrome and type 2 diabetes. I have a great group of researchers working with me and I love the camaraderie and intellectual challenge that comes from their interactions.

So what were the paths that led me to where I am now? I certainly didn't have it as my lifelong ambition but I wouldn't change it for anything – well not on a good day!!! My parents were very supportive but didn't have an academic background. I had a really inspirational chemistry teacher, so I went to university to study chemistry but found I had been given very bad advice from a careers teacher at school so ended up on a course mainly focusing on physical chemistry and maths. Also I lived with a group of arts students who were heavily into drugs. After 6 months, I took the rather scary step of leaving and reapplying for a Biochemistry degree.

After leaving university, I had to work to earn enough money to fund my new degree. I was lucky enough to get a job as a Research Assistant in the cardiovascular group at ICI pharmaceuticals (now

AstraZeneca). It was a wonderful time as I met some really inspirational scientists and much later married one of them. I was trained in a whole range of experimental techniques and worked on various drug discovery projects including follow-up compounds for the newly launched β -blocker, Propranolol (Inderal). It was during this time that Atenolol (now known as Tenormin) was identified in the pre-clinical testing cascades and I can still recall the excitement in the laboratory when the graphs were plotted showing the pharmacological properties that distinguished it from the previous β -blockers. It is now widely prescribed for patients with either hypertension or angina pectoris and considered a 'block buster' medicine. Prof. Sir James Black had the original idea to develop β -blockers, for which he was awarded the Nobel Prize. Although Jim moved from ICI, he became a good friend of the family and continued to challenge my science for many years. The laboratory was visited by some very eminent international experts on cardiovascular disease and it was quite daunting to show them our *in vivo* experiments (so I hope our eminent endocrinologists are kind to trainees when they visit labs!).

I was asked to set up some experiments to look at the effects of β -blockers on adipose tissue and was taught to prepare the adipocytes by a biochemist in a nearby laboratory. The head of the laboratory was Jeff Thorpe who was working on a hypothesis that would produce a lipid-lowering agent. The compound was due to go into volunteers, but Jeff was testing it on himself and I had the task of processing litres of urine each morning to assess its renal excretory profile!! His work

subsequently led to the development of clofibrate, a 'first-in-class' cholesterol-lowering drug. Fibrates are still widely prescribed today. Jeff's character, as described by his colleagues, was that he lived for science, but did things 'his way' and ran a 'one-man show'. That the ICI culture could tolerate such characteristics is a tribute to the manager of the biology section, Dr Garnet Davey. Other scientists working in the laboratories were Dr Raventos, a Spanish refugee pharmacologist who discovered the widely used volatile anaesthetic, Halothane. Another project was led by Dr Walpole, who worked on contraceptives. He identified a compound that worked in rats but was then found to enhance human ovulation, so couldn't be taken forward as a contraceptive. He thought it might work as an anti-oestrogen, and his pioneering work led to its application as Nolvadex in the treatment of breast cancer. These scientists were a group of exceptional drug hunters.

It was quite a summer and in retrospect I realise that I was very privileged to be amongst the discovery research at ICI pharmaceuticals at a time when four major new medicines were developed within a span of 15 years. I thought it was the norm to chat with scientists who were doing *in vitro* and *in vivo* experiments that led to drugs that had major impacts on patients' lives and to have research move at such a pace.

I have only subsequently realised that drug discovery doesn't usually happen like that. Since then I have collaborated with several pharmaceutical companies where the staff have not had an idea translated into a marketed drug in a 20-year career. It has left me with a conviction that scientists who make 'big' discoveries are not usually easy to manage and go their own way and often need a 'benign dictator' as their boss. Not something our major pharmaceutical companies do well.

The challenge for major pharma companies today is to cultivate a drug hunter culture that attracts risk takers with a critical knowledge of the cognate science and have a non-compliant attitude to formal organizational processes and are more ambitious for their project than themselves. Currently, Research Directors seem to be imprinted by the management consultant's addiction to tight project management and adherence to bar charts, failing to champion innovation because organizational management is easier. They must realise that it is individuals not directors who discover improved medicines. There is now a move away from research in large pharma and towards small units, but this will have its own problems, if it doesn't recognise the drug hunter culture.

My time in pharma research stood me in good stead when I got to university. I was in great demand as a partner in student practicals as I knew more about the calculation of concentrations and laboratory techniques than most of the demonstrators!

Looking back I realise that this necessity to earn enough money to support me through University exposed me to what we now call translational research. It made me want to address research questions that have an impact on human health. My PhD was a difficult experience with a male supervisor who bullied and harassed female students. I slowly became aware that there were also questions about the scientific rigour. For any student who is going through that now, it is unacceptable. However, it is strange how a supervisor's colleagues can't stop it happening. I've subsequently been a colleague of a similar scientist and it's so difficult to get enough evidence without harming the career of the student that I can see why people didn't intervene for me but I couldn't understand it as a student. Looking back on it now, I realise that I learnt to make my own decisions about research questions as well as developing important skills in how to manage 'negotiation' of controversial scientific decisions.

Working on hybrid cell lines with the aim of understanding what made them adherent and what caused tumour cells to move into suspension led me to study the proteins that are involved in cell adhesion, an area that subsequently became known as matrix biology. It was my skills in making hybrids that got me my first postdoc position. Monoclonal antibody production was in its infancy and although the procedures for producing the hybrids worked well for us the real challenge has and still is to get high affinity, high specificity monoclonal antibodies for hormone immunoassays. It seemed a bit unfair that while my contemporaries were publishing papers on the first antibody they produced, we made over 400 monoclonal antibody secreting hybrid cell lines and didn't find any monoclonal antibodies that would be an improvement over a polyclonal antiserum in a RIA. However, perseverance finally paid off and we produced the first monoclonal antibodies to progesterone and then testosterone and subsequently to vitamin D3. The chemist who made the immunogens was a recluse and only worked nights but was absolutely fantastic at making complex steroid immunogens by conjugating carrier proteins at specific sites on the steroid molecule. Some of these monoclonal antibodies form the basis of commercial kits used today and the royalties from the licence

agreements have funded many of my PhD students and much of the preliminary data for our grants.

This phase of my career happened to coincide with a miscarriage and subsequently the birth of our two children, interspersed with a number of operations. I think concentrating on my research took my mind off some of the more difficult times! I remember writing a paper on testosterone monoclonal antibodies just before one op and realising that the pre-med was having an effect on my ability to explain the specificity of the assay!

When the children were young, my husband was promoted to the board of a pharmaceutical company as the Medical Director, which had a marked effect on my career options. There are always good and bad sides to these situations. He had to travel a great deal so I was more limited in what I could do, but I had a lot of support from nannies, etc. so could often work late in the laboratory. As a wife of a board member, I was expected to entertain visitors' wives which was rather a shock and not very compatible with laboratory life, so I had a deal with my husband's secretary who took them sight-seeing for me. I also had to attend board dinners, which was very interesting as I met CEOs of major companies and my science background made for stimulating discussions. It has also helped in my subsequent roles for the University. However, I didn't appreciate the fact that the wives were asked to leave while the males passed round the port at the end of the dinner!

It is difficult to fit in a research career with having a family and although some women seem super-human and able to 'do it all' there were times when I found it difficult. I still can't decide whether that is because of the way women do science compared to men or because there are so many dual and often conflicting demands on their time. For younger scientists who may be facing these issues, I would reassure them that it is really worth persevering and you can 'have it all'! You do need a support network and that can come from various different avenues of your life, so don't be afraid to look for them and find mutually beneficial arrangements. However, it does mean that you may need to read the literature while at the swimming pool and write lists in boring meetings; after all women are good at parallel processing and those skills are essential for research.

My research group became very experienced in the nuances of designing immunogens and developing antibody characterisation assays and then putting together optimised immunoassays that could work in patient samples. As a result, we were asked to make monoclonal antibodies to insulin-like growth factors

and their binding proteins and this triggered 10-year research and some very interesting projects. I had great fun working with Melissa Westwood and Martin Gibson who were fantastic students and are now senior faculty members in Manchester. We attended some stunning conferences and made great friendships along the way.

However, the more important discoveries have come from the research we did as a result of making monoclonal antibodies to ACTH and its precursor pro-opiomelanocortin (POMC). Initially, we developed monoclonal antibodies to both the N- and C-terminal regions of ACTH, which enabled us to develop a two-site assay that was more specific and a thousand fold more sensitive than radioimmunoassays based on the single monoclonal antibodies.

We then went on to make monoclonal antibodies to other peptides in POMC and this enabled us to develop a two-site assay for POMC itself. As a result of 5 years of technology development, we were able to show that most patients with the ectopic ACTH syndrome have ACTH precursors in their circulation at much higher concentrations than ACTH itself. We believe this is because their tumours are secreting ACTH precursors rather than ACTH and we are currently looking at POMC as a biomarker in patients with small cell lung cancer.

We also use our assays as tools in the differential diagnosis of Cushing's syndrome. This research led to numerous publications on POMC and ACTH precursors and glucocorticoid resistance in small cell lung cancer. We know that POMC is not inhibited by glucocorticoids in these tumours because of decreased expression of the glucocorticoid receptor (GR) and that increasing GR increases apoptosis of the tumour cells. We are still studying the role of glucocorticoids in small cell lung cancer. With Prof David Ray (a former PhD student) we have recently shown that the GR promoter is more heavily methylated which would explain the decreased levels of GR. That's what makes research so fascinating in that answering one question often triggers the next conundrum.

My interest in POMC and ACTH has led to a long-standing collaboration with Prof. Steve O'Rahilly, and I really enjoy working with his group in Cambridge. We have a mutual interest in understanding the pathway that processes POMC to MSH peptides in the hypothalamus and the implications for obesity. We have studied mutations in various peptides and processing enzymes in this pathway, which cause obesity in children. Distinguishing the role of POMC as a regulator of energy homeostasis in the

hypothalamus from its role as the precursor of ACTH in the pituitary continues to be a challenge.

Along the way, I have been able to take on roles that fit with my enthusiasm for graduate training (perhaps because of my own experience). I have championed the need to establish realistic graduate training courses both in my own University and nationally in the UK by working with our funding bodies. Many of the schemes we piloted in Manchester have now been rolled out to other universities and research institutions and I'm still dedicated to making these 'work' for students and not just be administrative tools to register compliance. So there are always challenges even for a Professor with an established post. Grown-up children still expect (and get) your commitment even if it's when you're on your way to a conference. Perhaps my biggest challenge is battling to keep time for the research when asked to be on so many committees. For me, the

research is addictive and I'm driven to solve the current puzzle – what a fantastic problem to have!

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Received in final form 1 May 2012

Accepted 4 May 2012