

# Sharpening the focus; the business of epithelial cell biology

An interview with Chris Potten

DAVID PEARTON\*

*Equipe Biologie de la Différenciation Epithéliale, UMR CNRS 5538, Institut Albert Bonniot, Université Joseph Fourier, Grenoble, France*

Dr Chris Potten is a singularly influential figure in the field of epithelial biology. His contributions have been seminal and include the introduction of the epidermal proliferative unit and of the concept of epidermal stem cells. With around 400 scientific papers and reviews to his credit as well as two books, he has certainly made his mark. His contributions have been recognised by the award of the Curie medal and recently the Weiss medal for radiation biology.

Dr. Potten graciously agreed to be interviewed for this Special Issue of *The International Journal of Developmental Biology*. This interview was conducted via e-mail during June -August 2003.

## **Can you give me a brief introduction to yourself? Your background, education, early scientific carrier, etc?**

My first degree was in Biology at the University of London and this was followed by a Masters in Radiation Physics and Radiation Biology at Guy's Hospital in London. Following that I moved to Manchester to the Paterson Institute for Cancer Research with which I have been associated for essentially all of my thirty seven years of academic research. I did my PhD under the supervision of Dr Alma Howard, who was the first to describe the cell cycle concept. This was in the field of radiation biology and involved studies of the pigmentation process in hair follicles and the consequence of exposure to radiation on the precursor cells for the pigment producing cells (melanocytes). Following the completion of my PhD in 1968, I went to America to do my first postdoctoral at Brown University which at that time was a major centre in skin and pigment cell biology. I then moved to a big general hospital in Pittsburgh for two years working

within a radiation biology group but having an interest in skin radiobiology although under the direction of a gastrointestinal radiobiologist. It was here that I started to become interested in the gastrointestinal systems. I then had a difficult choice as to whether to stay in the USA or return to England. I decided the latter since my two sons were born in the United States but we wanted them to have an English education, plus the fact that Professor Lasslo Lajtha, a leading authority on haemopoietic stem cells and the concepts of quiescence in the cell cycle ( $G_0$ ), invited me back to Manchester to form a new group working on epithelial cell biology. This I set up in 1971, and it grew to be a department of about up to twenty eight people over the intervening years. My interests within this group were in stem cell concepts as applied to epithelial systems (skin and gut). The identification and characterisation of these cells and their regulatory factors, their response to cytotoxic insults such as radiation and drugs, and the biological significance of apoptosis as applied in these systems. I had a growing interest in apoptosis following the visit of a scientist from Professor John Kerr's department in Brisbane and I believe we were instrumental in keeping the concept alive, together with a group in Edinburgh and a group in Brisbane during the 70's and early 80's, until the point that American scientists took the concept on board. In 1981 I was awarded a Life Fellowship from the Cancer Research Campaign, shortly afterwards I was an Honorary Professor within the University of Manchester. I have had visiting sabbaticals in the Dept. of Pathology in Brisbane, in the Department of Dermatology in San Francisco, in the Department of Pathology at Temple University in Philadelphia and for seven years I was a visiting Professor in the University of Florence delivering a lecture course in

\*Address correspondence to: Dr. David Pearton. Equipe Biologie de la Différenciation Epithéliale, UMR CNRS 5538, LEDAC, Institut Albert Bonniot, Université Joseph Fourier, Grenoble, France. e-mail: david.pearton@ujf-grenoble.fr

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**Dr. Chris Potten (circa 1980).**

cell biology. I have had collaborations with scientists in Germany, particularly a big biomathematical group, scientists in Japan, USA, Sweden, Australia and many other countries. I have now published about 400 full length scientific papers and reviews, edited eight books and written two. I have been awarded the Marie Curie medal for work in radiation biology and am due to visit the International Congress of Radiation Research in Brisbane in August to receive the Weiss Medal for my work in radiation biology. These two medals in radiation biology are a little surprise to me since I really regard myself as a cell biologist and not a radiobiologist! In the year 2000, I officially retired from academic research at the Paterson Institute and with my senior postdoc Dr. Catherine Booth we set up a company called EpiStem Limited which, over a period of two years, has grown from a staff of 4-5 to 17. It specialises in providing epithelial related technology to the pharmaceutical industry but we also have our own product development division. I am currently Chairman and Scientific Director of that company. Our website is [www.epistem.co.uk](http://www.epistem.co.uk).

**You started off in radiation biology? What inspired you to choose this particular subject?**

When I started in the field of radiation biology there was still considerable interest in the aftermath of the Manhattan Project and many of my supervisors and early associates had been involved at one level or another with the Manhattan project. Additionally, it was shortly after the Windscale (now Sellafield) nuclear accident in the UK and there was a considerable interest in developing specialists who could bridge the gap between radiation physics and biology.

**Who has influenced you the most as a scientist? Do you have any significant mentors who shaped the way you do science?**

There are a number of people that have had a major influence on my scientific interests over the years. These include, Alma Howard for her work on the cell cycle, Lasslo Lajtha for his work on

stem cells and the  $G_0$  concept, Herman Chase for his work in radiation biology of skin and biology of skin, Sam Leshner for his work on the radiobiology of the gastrointestinal tract, John Kerr for his work on apoptosis and, more recently, John Cairns for his interest in genome protection mechanisms in stem cells.

**You were instrumental in originating the concept of the epidermal proliferative unit and the epidermal stem cell. Can you briefly describe the process by which you developed this concept?**

The concept of the epidermal proliferative unit was published in 1974 and has withstood the passage of time and now appears in modern dermatology textbooks. The idea originated from my interest in hierarchical or lineage organisation of tissues and the fact that stem cells were rare but crucial cells in proliferating systems, combined with observations that were appearing in the literature in the early 1970's, indicating a high degree of structural organisation in murine and other rodent epidermis, with proliferative patterns associated with structural organisation. This was work that came out of Germany (Enno Christophers) and work in the UK from a dental department with Ian MacKenzie. I think what the epidermal proliferative unit concept did was bring all those ideas together and suggested a generalised scheme for all proliferative tissues. As with many things it was a paper that attracted quite a lot of criticism at the time since it went against the current view that all basal cells was equipotential. It also of course attracted quite a lot of interest.

**Other than the stem cell concept, what have been the most important conceptual advances in the area of epithelial biology since you have been involved in the field?**

It is hard to dissociate the stem cell concept from other advances when talking about the epithelial systems. I think that the two most obvious areas that are of importance are apoptosis and carcinogenesis, both of which have specific associations with the stem cell compartment. My particular interests in the apoptosis area was: what was the biological significance and implications of this type of death, in which cells did it occur, how did the tissue recognise that cell death had occurred and how did it respond, and what is the biological role of apoptosis. In terms of carcinogenesis, I think the important aspect here was the realisation that cancer is probably a disease of the stem cell compartment. I think the other area of importance has been the issue of why we do not get more cancers than are currently the case when you bear in mind the number of cells that are dividing over the length of our life-span. This brings in the concepts of genome protection and the recent rather controversial papers that have been published in relation to DNA strand segregation and the Cairn's hypothesis.

**What is your impression of the current status of the adult stem cell field? In what areas is our knowledge lacking and where do we go from here? What do you think are the short/medium term potentials?**

I think there have been some enormous advances in our understanding of stem cells over the last few years, not only the haemopoietic stem cells but stem cells in other tissues such as nervous tissue, muscle, liver, etc. A major question at the moment is the one associated with plasticity which relates intimately with the question of stem cell regulatory factors and processes and to what extent these can be controlled or manipulated by us as experimentalists or



**Chris Potten circa 1988.** *Dept of Pathology, University of Queensland. Studies into EPU structure and apoptosis in the wing membrane of the fruit bat.*

clinicians - these questions are important in terms of tissue engineering, wound healing, gene therapy etc. A really major area of interest I think for the next decade is going to be the role of stem cell damage, deterioration etc., with ageing. Do we age because we lose stem cells, or do we age because we accumulate stem cells with impaired functional capabilities? I think there is going to be a major issue as to whether adult tissue stem cells really do differ from embryonic stem cells. If we really understand the regulatory processes and the plasticity stories hold out with the passage of time, then it seems that adult tissue stem cells may have the ability to do virtually everything that we currently associate with embryonic stem cells. I think the production of transgenic animals such as 'Dolly the Sheep', indicates that cells can be reprogrammed to make anything in terms of tissue.

**You have left academia to start a new company. What is your opinion regarding the differences between academia and industry and the current trend towards more academic and for-profit industry collaborations?**

We formed the company, EpiStem Limited, as a consequence of the fact that in the last few years of my academic life I had been approached by many pharmaceutical and biotech companies to gain access through collaborative studies to our cell biological and stem cell biological knowledge and the stem cell related bioassays which we had developed. As a consequence of these interactions a large amount of money came into my department and we thought that there was a potential business to be had here. My academic research for many years had had the underlying brief to try and understand more about the regulatory processes which went on in tissues; the intercellular dialogue and communication processes. Our R & D programme effectively continues this interest using modern genomic based techniques but with the focus being more specifically directed towards identifying potential drug targets which would be of value in the treatment of cancer, rather than the much less focussed academic interests in trying to understand the processes. The long-term objectives are essentially the same but the research within a company environment is much more focused. In hindsight I find it curious that the UK cancer charities do not have the same focused clinical objectives in terms of ultimate drugs to treat the disease.

**Do you therefore think that more goal-directed funding from non-profit funding sources could help “democratise” access to future therapeutics? Is this a way to help alleviate the problems of prohibitively expensive treatments and stimulate research on “non-profitable” diseases?**

I am afraid that I do not think that the more goal-directed funding from non-profit sources would help alleviate the cost implications, since at the end of the day, the drug development process can ultimately be only achieved by pharmaceutical companies who then control the pricing. It is, however, possible that non-profit research funding organisations could perhaps influence the pharmaceutical companies in terms of their price structuring. However, knowing the power that the major pharmaceutical companies exert, this may be a vain wish.

**Currently in Europe and the USA there is a high degree of suspicion and apprehension towards many modern developments in the biological sciences, for example, genetically engineered foods, embryonic stem cells and therapeutic cloning. What, in your opinion lies at the base of this mistrust, and how can scientists help to ameliorate these concerns?**

This is a difficult question to answer. Some of the things that lie behind the current mistrust that the public has in modern technologies are as follows:

1. The excessive power, domination and profit driven motives of the large multinational drug companies.
2. The fact that scientists have little opportunities, or indeed skill in many cases, in putting over the case for particular developments.
3. A genuine apprehension about safety which in many cases has not been convincingly assessed.
4. The difficulty in many instances in balancing benefits versus risks.



**Dr Chris Potten (circa 1995).** *Chairman and Scientific Director of EpiStem Ltd.*

**Based on this, do you think there is a need for a mechanism, either government-sponsored or independent, for assessing risks and benefits associated with new technologies? Or can we trust the current system of regulatory bodies, peer review and corporate-sponsored trials?**

My concerns with the safety versus benefits issue really refers to the approaches that have been adopted to undertake clinical trials which are ostensibly controlled by the regulating bodies. My fear is that in some cases, trials are instigated based on over-optimistic expectations by the drug companies and insufficient preclinical validation and proof of principle studies. It is also quite common for trials to be instigated without a clear understanding of the mechanism of action of a particular drug.

**What advice do you have for young scientists who are currently at the beginning of their careers?**

To work hard, read thoroughly around the literature, particularly including some of the older literature - there is a remarkable tendency for concepts and results to be reinvented 20 or 30 years after they were originally described, and also to realise as soon as possible that scientific research rarely, if ever, provides definitive answers. The best that can be expected is an approximation to the truth. The better the experiment, its interpretation and analysis, the closer one gets to the truth.

**What is the most important attribute that makes a successful scientist?**

An ability to think imaginatively and to bring innovation into a particular scientific project.