Were it not for an experiment that had apparently gone wrong, Margaret Buckingham, a professor in the department of developmental biology at the Pasteur Institute in Paris, France, may have never discovered her most important contribution to the field of cardiology. When Buckingham and her colleague Robert Kelly saw an unexpected expression pattern of a myosin transgene in engineered mice, they did not scrap the experiment and start over, but instead they investigated more closely.

The transgene, they later discovered, had integrated into the gene for fibroblast growth factor 10 (Fgf10) and had inadvertently become an excellent marker for a population of heart progenitor cells. Until that point, it had been assumed that the mammalian heart arose from one population, or field, of embryonic cells. The work of Buckingham and Kelly showed that there were, in fact, two quite separate heart fields, deriving from two myocardial cell lineages.1–3 These discoveries changed the way biologists thought about normal heart development and about how congenital heart defects might arise.

Buckingham said, in a recent interview with Circulation Research, that having a keen eye and not immediately dismissing aberrant results as artifacts are two important aspects of scientific endeavor. So, too, she added, is an unwavering perseverance.

In addition to her heart development work, Buckingham studies skeletal muscle development. One of the key differences between the two muscle types, she showed, was in the upstream cell fate decision-making factors. One of her other major discoveries was that a family of transcription factors encoded by Pax genes drives the cell fate choices in the early embryo that eventually lead to skeletal muscle formation.4,5 In both the heart and skeletal muscle fields, therefore, Buckingham has been, and continues to be, a leading light.

Where Did You Grow Up?
I spent the first 8 years of my life in Oxford, UK, where my father was a philosophy don [at the University], and then, since he was a Scot, we moved to the North of Scotland and I spent my subsequent childhood in Aberdeen.

When Did You Know That You Were Going to Study Science?
At school, I mostly studied Greek, Latin, and mathematics, and actually I got into Oxford University partly on that basis. However, I was an avid reader of the Scientific American and was also inspired by a marvelous BBC program about the living cell, made by biologist Michael Swann. Also, in my small school in Aberdeen, we had a very good biology teacher who would tell us about the latest developments, the genetic code, that kind of thing.

I was not the only one to be inspired by Miss Forster. There is a celebrated mouse embryologist called Kirsty Lawson who was also taught by her.

The moral is, if you happen to have the good luck in school to be taught by a teacher who is really enthusiastic, then that can affect the course of your life.

When Did You Know You Wanted to Study for a PhD?
When I was at Oxford—this was the 1960s—there was much excitement over the discovery of messenger RNA and how the genetic information was translated into proteins. That work, of course, came from Monod and Jacob in Paris, but in Oxford there was a group of people working on histones and how histone modifications might affect the way the genetic
information of the cell was read. I was excited by this general area of research and decided to do a PhD with Dr Ord, in that group.

People Tend to Think of Histone Modifications as a Relatively New Area of Study...
Yes, it is something that has come full circle. Back then, of course, there were not the tools to look at things precisely, so most of the work consisted of correlations. More recently the histone code, as it is called, has become a major subject and people have much more precise ways of looking at the consequences of histone modification. It is nice to see that some of the predictions we made from our correlations—for example, that histone acetylation drives transcriptional activation—have proven to be correct.

Why Did You Move to Paris?
It was because of the exciting work that was coming out of the Pasteur Institute at that time on messenger RNA. It was also because I was interested in painting and, as you know, Paris is associated with famous painters and it still had, and has, great studios where you could go to draw and paint live models and learn from your peers.

Subsequently, when I had children and when I was fully occupied with my scientific career it became impossible to do too many things, so I had to let the painting drop.

Why Did You Choose Developmental Biology?
What excited me was how genetic information is selected when a cell assumes a differentiated phenotype. Initially, one could not look at that easily in vivo. So, when I came to the Pasteur Institute to work with François Gros, we used skeletal muscle cell lines. But with the advent of genetic engineering and the possibility of making cloned probes, it became feasible to look in the embryo. My laboratory was one of the first to begin studying patterns of gene expression during skeletal myogenesis in vivo and that led us to ask questions about regulatory mechanisms.

We also looked at the structure of the genes that were involved in myogenesis. Many of the genes expressed in skeletal muscle, such as the myosins and the actins, are also expressed in the heart, which is how we began to look at things in the heart.

Did You Ever Consider an Alternative Career?
No. I mean, I would like to have had several lives. I would like to have had one life where I did painting and one where I pursued my interests in Greek and Latin and ancient history, or did archaeology. However, given that I just had one, I am not displeased with the fact that I did science.

Have There Been Any Low Points in Your Career?
The really bad moments are when technically things will not work and it is probably because the techniques are not quite up to it and not reliable enough. Those are the real moments of frustration.

Then, when you come to direct a laboratory, a major anxiety is for the young people for whom you are responsible because their professional lives depend on having really good publications and, of course, one can never predict what line of research will hit a technical brick wall. It is not at all a reflection on the quality of the young person, it is a problem with what works and what does not. Those are the kind of things that keep me awake at night.

How Do You Encourage Your Staff to Overcome Such Technical Difficulties?
Partly, I think one has to have a great deal of perseverance to be an experimental scientist. You just should not give up. You should keep trying. Then, eventually, when things are really not working you have to be flexible about other approaches.

I would also say that one has to be extremely attentive. Our transgene Fgf10 experiment is a good example of that. By observing carefully, you can sometimes get a clue as to why something is not working, or you can get a major scientific clue about something you never thought about.

What About Just Plain Hard Work?
I never thought of myself as having a job. I always thought I was lucky enough to get paid for what I liked doing. So, I guess I have always rather had the attitude of a postdoc with a fellowship, and I certainly have always worked very hard.

I usually work at home at the weekends, on papers or grants, and when I was younger I used to work long hours in the laboratory, basically because I just thought of it as doing what I was interested in doing.

How Do You Juggle Science With Family Life?
My three children have now left home, but it used to be a bit of a balancing act. I had the good and necessary luck to have a husband who shared everything in the way of family life with me. He is also a scientist. Of course, we could never go away to meetings together, if I went to a meeting, he stayed and looked after the children and we sort of juggled it like that.

I had my children when I was slightly older—I was about 35 when my first son was born—and by that stage I could afford to have somebody who was at home and was always there to look after them. Along this line of thought, it grieves me that many really good young women scientists stall at the point when they should be going ahead and having their own groups.

How Would You Encourage Them to Stay?
Well, I think they should not be put off by the apparent difficulties. You have to have a lot of energy, of course, and you have to be convinced that you can do it, but I think it is also a question of confidence. And women often are not as confident as men. My young female colleagues sometimes do not feel that they want to be put into a situation where they have to constantly overcome the difficulties, which we all face. Anyway, I also note that many of them, fortunately, do take on this challenge and that is very good and I try to encourage them as much as I can.

Have You Ever Been Tempted to Return to UK?
Well, there were job offers and I was tempted, but by that time my children were older and were horrified by the thought of leaving their friends and environment, and since
when I was a child I had also been horrified at leaving Oxford to go to the far North of Scotland, I thought I could not do that to them.

References


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Ruth Williams

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