



EDITORIAL

A MESSAGE FROM PROFESSOR MARK HANSON, WHO WAS AWARDED THE RECTOR'S MEDAL OF THE UNIVERSITY OF CHILE IN JUNE 2016.

Mark Hanson¹

¹Institute of Developmental Sciences, University of Southampton, UK

I was given a copy of Charles Darwin's "The Voyage of The Beagle" (which appeared initially in 1839 but not published as this title until 1905) in 1963. I was fourteen years old and was just beginning to think seriously about a career in medicine and science. When I read of Darwin's observations during his travels in Chile, I learnt for the first time how comparison between the biology and the culture of different countries could yield very deep insights. This was clearly the case for Darwin, not only in his famous comparison between the finches on the various islands of the Galapagos, but in his speculations about the geology, history and culture of Chile, different from anything he had encountered in England.

It would not be until almost thirty years later, however, that I had my first opportunity to visit Chile, at the invitation of Professor Anibal Llanos at the University of Chile in Santiago and with the encouragement of my then PhD student (now a Professor in the University of Cambridge) Dino Giussani. We had obtained a small grant from The Royal Society in London to make the visit possible. I hardly knew what to expect as I stepped off the plane in Santiago. My school education had taught me nothing about South America and I spoke no Spanish. What followed was undoubtedly one of the most important chapters in my career.

Dino and I had been studying the mechanisms underlying the responses of the fetus to episodes of acute hypoxia in the sheep, using a model in which the fetus was chronically instrumented to allow a range of physiological variables to be studied in the conscious animal over the course of many days. We were able to induce acute hypoxaemia in the fetus by giving the pregnant sheep a low oxygen gas mixture to breath, usually for a period of one hour. Our results had important clinical relevance, as the level of hypoxaemia we induced was similar to that experienced by the human fetus during labour and delivery, and there was considerable interest in finding measures such as heart rate

variation that would indicate whether the fetus was coping well with this challenge or should be delivered.

Revealing though these studies were, we knew that there was another aspect of the story which we were ignoring. The problem of fetal growth restriction was, and still is, very important, not only for short term survival of the baby but because it was at that time becoming appreciated that low birthweight babies had a higher risk of cardiovascular disease and diabetes in later life.

Ultrasound-guided blood sampling from the growth restricted fetus showed that such fetuses were similarly hypoxaemic to our sheep fetuses. It was clear that we needed to study not only the effects of acute hypoxia on the fetus, but also those of chronic hypoxia sustained for many weeks of gestation. Furthermore, we needed to find out how such chronic hypoxia would influence the response to the acute hypoxia which the fetus would be likely to encounter weeks later during birth. Would the fetus adapt to the hypoxia, making it less susceptible to the subsequent hypoxia, or would the chronic hypoxia lower its ability to respond to the acute hypoxia, making it at greater risk and perhaps more likely to need to be delivered? We had no way of answering this question in London, at sea level, where it was impossible to induce hypoxia for such a long period of time in our large animal model.

So started a collaboration with Anibal Llanos and his group. Together we showed the effects of living at altitude on the fetal and neonatal responses to hypoxia, in terms of reflexes, endocrine and paracrine processes. Always inventive and always ready to take the studies to the next level, Anibal's team investigated the molecular processes underlying these responses in different tissues in both the llama and the sheep. The studies are now on the verge of uncovering the epigenetic basis of some of these processes and of piloting novel treatments to prevent the damaging effects of hypoxia. I cannot do justice to the importance of this long series of studies by trying to summarise them in a





few lines, but I urge students to read them as an example of scientific rigour and thorough investigation, all directed towards improving understanding of human health. Instead, I would like to record some of the things which I learnt during what is now twenty five years of collaboration with my Chilean friends.

The first lesson, which was immediately apparent to me in the early 1990s, is that it is possible to conduct good science even with very limited resources. Resources in terms of equipment and facilities were indeed somewhat limited in those days, after a period of very difficult times for Chilean society. But if one asks the right, answerable question, and is willing to work hard, progress is possible. For Anibal Llanos and his team no effort was too great and the time commitment was irrelevant. When they demonstrated what they could achieve, we were able to convince external bodies such as the Wellcome Trust to fund their work, and sustained support has also come from Chilean scientific bodies to endorse this point. What a great demonstration of what Peter Medawar called “the art of the soluble”!

For the second lesson, I had an inkling of the message as it was partly the reason which first brought Dino and I to Chile – namely that great insights can come from thinking laterally, across borders, whether they are scientific disciplines, species, developmental stages, or continents. I had not expected what we learnt from this lateral thinking to be so revealing. The smaller the intellectual box in which we confine ourselves, the more limited the vision we will have. For those readers early in their careers in medicine and science, the future will be much more cross-disciplinary than my early experiences were, and those who can culture the skill of thinking outside their box will in my view make the greatest contributions.

The last lesson I would like to highlight is a personal one. It is to record my immense gratitude to my Chilean collaborators for their enduring friendship over the years. Biomedical research is highly competitive, as perhaps it should be to maintain standards, and gaining funding and getting work published can be very tough, especially if we are breaking new ground and challenging accepted dogma. It is also extremely hard work. What makes it not just bearable, but actually a real joy, is to work with collaborators who are friends¹. Such friendship makes the frustrations of research easier to bear, and the successes even more rewarding.

Darwin would have understood very well the insights we gained from comparing the responses to hypoxia of the llama, evolved for life at high altitude, with those of the sheep, a newcomer to the altiplano. I re-read some of Darwin’s “The Voyage of the Beagle” before I came to Chile this year, and noticed something I had missed. Darwin was in Chile at the time of the devastating earthquake in Concepcion in 1835. He was impressed and shocked by the enormous refiguring of the landscape which such geological upheavals could produce. Then, pondering the layers of shells which he found lifted above the coastline and even in the Andes, he realised that they must have been laid down by a series of such dramatic events over a vast period of time. The timeframe might not be so different from that which deposited layers of fossils in his native English coastline, as shown by his friend the geologist Charles Lyell. We can see his thinking about how species as well as landscapes might change over epochs. This led to some of his early scientific publications and of course eventually to his ideas about evolution. Chile has a long history of scientific and cultural achievements and a long history of inspiring its visitors. I am very grateful that I have been given the opportunity to be involved in just a tiny way in that continuing tradition.

¹ I was very saddened to learn recently of the death of Dr. Raquel Riquelme who was such a pillar of strength in Anibal Llanos’ lab and a great friend to us all.

