

An interview with Claudio Stern

ALEJANDRO SANCHEZ ALVARADO and CLAUDIO D. STERN

ACCEPTED MANUSCRIPT

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Title: “An interview with Claudio Stern”

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ABSTRACT

Claudio Stern was born in Montevideo, Uruguay where he received his school education. He moved to the United Kingdom at age 18. This interview briefly explores his trajectory from Uruguay, through universities in the UK (Sussex, UCL, Cambridge and Oxford) and USA (Columbia) and how he was influenced by various mentors and experiences.

Claudio, when you reflect upon it, can you pinpoint a time in your upbringing as a young boy in Montevideo, Uruguay that you can say “that’s when my interest in science began”?

I wonder if it was always part of my inner nature. I was fascinated by creepy-crawlies and the wonders of Nature since I was a very small boy (Fig. 1). I was always staring at the ground, looking for interesting things. When at primary school, I collected butterfly pupae and watched them hatch at home, once I even made a home movie of that process. I also enjoyed playing with a chemistry kit (one time I nearly set the house on fire) and trying to learn the names of the stars, so I guess I was interested in all areas of Science! But my inner passion was really about living things, including the human body.

Since I am asking you to recollect, if I may be so bold, when did you read Darwin for the first time?

I remember reading Darwin's account of his extraordinary trip around the world, “Voyage of the Beagle” when I was at school. I was drawn both by his adventures like the account of his horse getting entangled when he was being shown how to use “boleadoras” (leather-wrapped balls connected by leather straps, thrown into the air to catch the ñandú, South American ostrich) and by his keen observations of nature around him. It was also interesting to read a contemporary view of the politics of the River Plate in the 1830s, when General Rosas was in power in Argentina. I got a copy of “The origin of species” soon after that I think, and later hunted for old copies of his other books (“The ascent of man”, “The expression of the emotions...” and others) at the Sunday Tristán Narvaja Street flea market.

I understand that you started your university education in 1971 at both the school of medicine and the Faculty of Science in Montevideo. I find this unusual. What prompted you to pursue a double degree?

I really wanted to make a career in Zoology, but my parents felt that this was not a good choice and persuaded me to study Medicine. This was not a problem since I was just as interested in the workings of the body and the whole of what we now call “biomedicine”. Fortunately in Uruguay at the time many of the classes in the Faculty of Science were held in the evening, to allow students who needed to work during the day to pursue an education at the same time. I took advantage of this and attended many courses in the evening while I was a medical student during the

day. I had started to attend the Faculty of Science in my last year of secondary school (Preparatorio) and continued during my one and only year as a medical student before I left Uruguay in 1972. But I did learn a lot in those two years.

Given the tempestuous and, quite frankly, dangerous period of upheaval in Uruguay in the early 1970's, you decided to quit your studies in Montevideo and leave your country to start from scratch in the United Kingdom in 1972. I wonder, why did you choose the UK in general and the University of Sussex in particular?

I guess it was mainly due to circumstances. I had been lucky to travel to the USA and Europe earlier and felt drawn to European culture, and also very much liked the British approach to everything. Partly this was probably due to my having studied English language at the Instituto Anglo in Montevideo, but also because my mother had become a keen reader of English and Irish literature (and a devotee of James Joyce). However my English cannot have been very good then, since I failed my first attempt at the Cambridge certificate (Fig. 2), which I later had to re-sit.

The system of university admissions in the UK was handled by a body called UCCA (later UCAS) where one could choose five universities in order of preference. I had been given some advice by the British Council (in retrospect much of that advice was very bad!) but there was something about Sussex that attracted me, perhaps partly because of its rebellious spirit as a “new” university (at that time it was barely 10 years old) and with high ambitions. I was particularly lucky in retrospect, although I did not know it at the time, that Sussex was then a boiling cauldron of excellence in Developmental and Evolutionary Biology, while the legendary John Maynard Smith was Dean of Biological Sciences.

What was it like to arrive as an immigrant in the UK in 1972? Could you please share with us some of your experiences?

I travelled from Montevideo to Europe by ship – an Italian transatlantic of the “C” line, destined for Genoa. The two-week voyage was extraordinary, and one of my memories is sharing the first few days with Vinicius de Moraes who was travelling to the port of Santos in Brazil – he played the guitar through the night, while all of us young people sat on the floor around him. Magic. I arrived in Nice and then crossed France by train to Dieppe, where I then took the ferry to Newhaven. I arrived late at night, with five suitcases (my mother wanted to make sure I had everything!) and it was a bit of a shock. Eventually, I made it to Sussex where it was all dark except loud noises from the bar where everyone was crowded, drinking beer. It took me a while to start finding my way. After the first few months, it became easier to make friends and start to adapt, even though I was finding it difficult at times to understand some of the lectures (for example I remember puzzling about what “nuclei” meant before I realised that it was the plural of “nucleus”!). Very quickly though I got to enjoy not only the British attitude to life and the Arts and Sciences but also the greatly multi-national body of students who had come from all over the world. This was very different from my education in Uruguay (Fig. 3), and it was great to learn about many remote countries and cultures, share a kitchen with people cooking all sorts of national dishes in traditional ways and more.

Why did you choose to study early embryogenesis? And of all systems you could have possibly chosen to study this in general, and gastrulation in particular, when and why did you decide to use chickens?

As an undergraduate, I was drawn to Developmental Biology because I was fascinated by how biology generates "complexity". How does a bunch of cells (all with identical genetic material, therefore identical information) manage to generate something as extraordinary as a whole body, correctly proportioned, every time? Where is the information for this process encoded, and how is it interpreted by the cells? For my PhD, I explored many labs (in the UK and USA), but in the end, I decided to stay at Sussex and join Brian Goodwin who offered me a place in his rather eclectic lab. No two people in the lab were doing the same or working on the same organism as each other. Vernon French was working on cockroach limb regeneration, Malcolm Maden on amphibian limb regeneration, Stelios Pateromichelakis on regeneration of the cap in the unicellular plant *Acetabularia*, Lür Willnecker on the generation of pigment patterns in the wing of the moth *Ephestia kühniella*, Kees Weijer on *Dictyostelium* aggregation, and others working on early *Xenopus* embryos. I was given an even wider choice of topic for my PhD, including "the chick" and "gastrulation" and picked that. The idea was to test an initial observation made in the lab by Jonathan Cooke who had been on sabbatical just before, that during chick gastrulation cells migrated in pulses similar to *Dictyostelium* aggregation perhaps implying chemotactic guidance of gastrulation movements. Things turned out to be a lot more complicated in the end, but also a lot more interesting.

I am going to assume that your initial forays into science in Sussex required a great deal of resourcefulness as Brian Goodwin was not working on chicks at the time. How much do you think your upbringing in Uruguay did or did not influence your approach to science, which I believe is characterized by a great deal of resourcefulness, creativity and skills?

Being in a lab so diverse offered a multitude of opportunities and lots of colleagues with whom to discuss ideas. A particularly outlandish one was inspired by an old paper where they had used *Dictyostelium* (the individual amoebae aggregate by chemotaxis to pulses of cAMP) as an assay to detect gradients of cAMP in frog embryos (Nanjundiah, 1974). Kees Weijer and I tried to invent a device that could sustain a very steep temperature gradient (from 20°C to 38°C in a millimeter or two) to see if we could use the same assay to detect regional differences in cAMP in the chick. It didn't work, but it was a good idea!

In my main project, I also had to come up with various inventive ways to solve problems. I was given a World War II 16mm camera (Vinten) for time-lapse movies and had to rig up various ways to put it on a microscope, control the temperature and more. It was very early days of computers, and I used one of the very early Apple IIe personal computers to control various devices as well as to analyse some of my results. It was great fun – made one feel like a real explorer.

For culturing embryos, I read the paper by Denis New (New, 1955) and tried to reproduce the method. I was unable to produce smooth rings by bending a solid glass rod well enough, so instead decided to produce flat rings by cutting them from a glass tube. This turned out to be a major advance over New's original method

because it allowed the vitelline membrane to grip and thus the ring to be lifted out and placed in an optically clear culture dish for filming. However, until a few years later, when I arrived in Ruth Bellairs's lab to see the original version of New's culture system, I had not appreciated the difference. I was particularly pleased that later on, Ruth's lab adopted the flat ring and culture dish method instead of round rings and watch glasses inside a Petri dish.

You have been an early adopter and a consistent proponent of using theory and models to help inform experiments and our understanding of complex biology. To what extent is your appreciation of models influenced by the words of Waddington, whom I have heard you speak of in the past with great eloquence?

Brian Goodwin had been trained as a physicist and was an extraordinarily gifted mathematician, renowned for modelling. After this, he became Waddington's PhD student in Edinburgh and later became a member of the influential group that met to discuss mathematical models of biology at Villa Serbelloni on Lake Como in Northern Italy. Other members of that group were also at Sussex during my time, including experimental psychologist Chris Longuet Higgins and evolutionary biologist John Maynard Smith, so there was a strong concentration of mathematical biologists around. Furthermore, we were frequently visited by other theoreticians who were coming to spend a sabbatical year, and they were always a source of inspiration. I learned to write code (Fortran, Basic, ALGOL-68, Pascal and machine language for the 6502 processor) and tried my hand at modelling for a while, but I wasn't very good at it. But I did greatly admire those who could.

Waddington was on a quest of "a universal theory of everything" and dabbled with many things. To some extent, Brian adopted some of this philosophy and wanted to find a short, clean mathematical expression that might encapsulate, re-describe and ideally predict the behaviour, of developing systems. All of us have looked upon physicists with considerable jealousy – for example how a very simple expression such as $(m_1 \times m_2)/d^2$ can predict so accurately the force of gravity and how this was arrived at so elegantly by Isaac Newton. If only one could do the same for development !

Did you ever meet Waddington?

Unfortunately not. In 1974 while I was still an undergraduate I joined members of my class to a discussion meeting at the Royal Society and "Wad" (as he was generally known) was sitting at the front and I think he asked some questions. The next year I started my PhD and wanted to meet Wad, so had bought a ticket to Edinburgh only to find out, on my way to the station, that he had just died (for a fuller account of this and more on Waddington see (Stern, 2000, Stern, 2013)). But I was very touched when I was awarded the Waddington Medal by the British Society for Developmental Biology (Fig. 4) – this held a very special meaning for me.

Could you please tell us a little bit about your academic mentors, Dr. Brian Goodwin and Dr. Ruth Bellairs? And also, could you tell us how they influenced you as a scientist?

Brian and Ruth were both in Waddington's "lineage": Brian as Wad's student, whereas Ruth had been mentored during her PhD by Michael Abercrombie, the noted cell biologist who had been a long-term colleague and collaborator of

Waddington's. But the two could not be more different from each other. Brian strongly believed that genes were virtually unimportant in regulating development, which was almost an obsession. He explored dynamics, bioelectricity, small molecules and other possible ways in which information could be carried to generate order and complexity through his deep, creative thinking but relied on experiments done by others. In his lab, everyone had the freedom to explore different avenues, but most of us were encouraged to think of non-genetic ways in which the process could work. I find it somewhat amusing that all of this is now making a strong comeback, when it was very much at the fringes of "acceptable" Science at the time.

Moving from Brian's lab to Ruth's, in the Department of Anatomy and Developmental Biology at University College London, was a major change in many ways. Ruth was a consummate experimentalist. She had huge manual dexterity and skill, seemed never to tire when working very long hours at the microscope, she knew the embryological literature in enormous detail, and was a superb microscopist. Ruth was responsible for discovering in the 1950s that the definitive (gut) endoderm arises from the ectoderm via the primitive streak rather than from the early hypoblast as was previously thought (Bellairs, 1953a, Bellairs, 1953b, Bellairs, 1955, Bellairs, 1957). She was also an early pioneer in the use of Electron Microscopy to study embryos. With her and many careful students and postdocs in her lab, I learned about experimental rigour, as well as a lot about histology and embryo anatomy. Ruth also taught me a great deal about interacting with colleagues and being an academic. Working with extremely different people, with different approaches and philosophies, can be a hugely enriching experience.

Could you share with us what your experience was like at Oxford when you were there?

After University College I spent a year in Cambridge as an Anatomy demonstrator, then was appointed University Lecturer in Human Anatomy in Oxford where I spent about nine years. It was in Oxford that my career flourished, despite a significant teaching load (about 12-15 hours per week contact time, including Human Anatomy, Histology, Embryology and more for the department, and regular tutorials, admissions interviews for my college, Christ Church). Oxford was a unique environment, and I hugely enjoyed interacting with colleagues across all disciplines. The colleges greatly facilitate that. It was also a place to meet extraordinary, legendary individuals. Regular visitors to dinners included Edmund Hillary the Everest pioneer, Richard Doll who first proved the connection between smoking and cancer, Rowan Williams (who would later become Archbishop of Canterbury), and many, many others. Teaching tutorials in small groups (of 1, 2 or a maximum of 3 people) is a learning experience for both the tutor and the students that this is what makes the collegiate universities like Oxford and Cambridge so special. For that reason (and a few others) many never move away – in 1993 when I was being recruited to Columbia University in New York my college colleagues could not understand why I might want to leave Oxford. It was the right decision, but I still miss many aspects of Oxford.

You have received many recognitions for your groundbreaking work, Claudio. Of these, and because of its remarkable history, would you mind sharing with us your experience of being selected a Fellow of the Royal Society? How were you

informed? How did you prepare for the day of the induction? How was the ceremony?

That remains probably the most rewarding experience of my career. The Royal Society is the world's oldest and probably the most prestigious scientific academy, having been founded in 1650 by figures including Robert Hooke (inventor of the microscope and much more) and Christopher Wren (who built St Paul's cathedral) and has hosted many extraordinary scientists from the UK, the Commonwealth and from all over the world. Only 44 new fellows were elected each year, from across all sciences and a very wide geographical base, from sometimes close to 1000 candidates proposed. The system has now changed, but in 2008 when I was elected, it was normal for the Fellows to be notified of the names of those newly elected before the candidates themselves (who were notified by a letter arriving by post!). I was surprised one day to arrive at home and find the answering machine full of messages like "Congratulations my boy, well done – although I am not allowed to tell you why!" from Lewis Wolpert, Jim Smith, and others and I had to connect the dots. That was only the beginning of a journey.

The culmination of the election procedure is the induction itself and the signing ceremony. For two days, newly elected fellows are cloistered in a room in the Society and give talks to each other at a level comprehensible to other scientists, which really brings home how amazing these colleagues are. The third day there is a tour of the amazing library and introduction to the history and work of the Society, then a very nice lunch for new fellows and their guests, followed by the signing event (Fig. 5). Then, we still had to do it with a goose feather dipped in Indian ink and the staff were paranoid that we might spill this over the wonderful red leather-bound book that contains the signatures of Charles Darwin, Albert Einstein, Isaac Newton, Waddington of course! The same book has still been in use for more than 350 years, and to sign it is a very special moment that makes one feel very, very small, but also very privileged.

That being said, do you think awards are important? Why?

I think it is important to feel that one's work is appreciated. Perhaps this is now more true than ever, since citations have completely lost their meaning (if they ever had one as a measure of originality, rigour or excellence) as people increasingly cite reviews, more recent rather than ground-breaking papers, and often without reading the source. It is important to have awards for different types of people and different types of contributions. However, I also think that a lack of such awards should not be used to judge colleagues – not only because of geographical and other differences in the number of awards available, but also because so comparatively few of the excellent people can be recognised this way. There is also some randomness in the process of who gets nominated and for what. I view it as a duty for all of us to identify appropriate awards for our deserving colleagues and helping them as much as possible to succeed with their nomination.

Of all your many scientific contributions, which one would you consider the most significant and why?

In a way, all contributions are significant in some way. "Significant" can be a value judgement, an opinion. Sometimes it is difficult to measure the influence of a discovery without considerable hindsight of time. Sometimes the apparent influence is inflated (or the reverse) by current trends, irrespective of the degree of originality.

I was lucky to be involved in a number of discoveries that gave me great pleasure at the time. They include the discovery with Roger Keynes that somites are subdivided into anterior and posterior halves and that this dictates segmentation of the peripheral nervous system (Keynes and Stern, 1984) (Fig. 6), finding self-renewing stem-cell-like cells in the node of normal vertebrate embryos that contribute progeny to the notochord and somites (Selleck and Stern, 1991, Selleck and Stern, 1992), collaborative work with Cliff Tabin's lab where we discovered the first genes involved in left-right asymmetry (Levin *et al.*, 1995), finding that FGF initiates neural induction events even before gastrulation (Streit *et al.*, 2000) and others.

These are quite well-known papers. But perhaps there are some others which I particularly value, but I feel that the message has not yet sunk in enough. One example is a small series of papers that examine the relationship between gene expression and cell fates (Stern and Canning, 1990, Izpisua-Belmonte *et al.*, 1993, Joubin and Stern, 1999, Streit *et al.*, 2000): these papers examine different aspects of cell behaviour in early embryos in different ways, but they all show that as cells move around the embryo they change the genes they express according to their current location. The message that comes out loud and clear from these studies is that "gene expression marks cell **states** rather than cell **fates**" (perhaps most directly demonstrated in (Joubin and Stern, 1999)), and that the study of developmental processes like cell specification needs explicitly to address *the difference between what a cell can do and what the cell does do*. Some modern single-cell RNAseq type experiments seem to overlook these important principles (see Stern 2019 – in press).

Could you share with us what ongoing research in your lab you are most excited about it and why?

We currently have four major lines of work in the lab, and I am excited by all of them! One big project concerns how the very early embryo breaks its radial polarity and decides where to place the primitive streak (often erroneously called "establishing the anterior-posterior axis") – this is particularly interested in amniotes like the chick and non-rodent mammals which can form identical twins (more than one individual from an initial embryo). For this, we are combining chick embryology with human population genetics and more. A second project has the ambitious task of uncovering the major gene regulatory interactions (ideally predicting ALL transcription factors and their interactions) involved in the process of neural induction, with a very fine time course. This involves detailed molecular biology work and complex bioinformatics but also taking advantage of an *in vivo* system where the time elapsed in the inductive interactions can be precisely controlled. A third project extends the work started by Mark Selleck in my lab in Oxford 30 years ago and aims to characterise the cells that have resident, self-renewing properties in the node of the embryo, to identify their niche and their behaviours, doing experiments at single-cell level. The fourth project returns to segmentation. While most of the literature in this field has been interpreted to support a "clock and wavefront" model to control the size of segments, we have made several observations suggesting that

the role of these clock-like oscillations may be mainly to establish the succession of anterior- and posterior- (rostral and caudal) half-somite identity, at least in amniotes, and that the periodicity of somite size may be determined mainly by other mechanisms (Dias *et al.*, 2014). Cell lineage history (perhaps the cell cycle) (Primmitt *et al.*, 1988, Stern *et al.*, 1988, Primmitt *et al.*, 1989, Collier *et al.*, 2000) may be important, along with mechanical constraints. These are all the very same questions I started to ask when I was a PhD student. and it feels that now, 40 years on, we are just starting to catch the first glimpse of some of the answers!

Finally, Claudio, what do you think are the future prospects for life sciences in Latin America?

I have great expectations that Latin American sciences will undergo a major transformation in the near future. My optimism in this regard is due to many factors. First, on the negative side, that a lot of the rest of the world is so heavily dominated by opinion and anti-science trends (like “fake news”, climate change denial, and more). This is coupled by primary school education moving more and more towards instilling great self-confidence in everyone's opinions even if they are not backed up by facts, and further fuelled by some social media like Twitter which allows only the briefest messages without any evidence. Reading the primary literature and scholarship is in decline and there has been a significant change in the motivation of young people in Europe and USA to study biological sciences: from genuine curiosity in the processes, as we used to have when I was a student, to mainly being driven by personal ambition and opportunism. Whenever I encounter young Latin-American scientists I am generally impressed by the degree to which they still do have that burning curiosity. Perhaps this is because those that are attracted to, and stay, in the Sciences are more motivated than in other parts of the World, but the result is remarkable, and this generates very high quality scientists who really think and who are enthusiastic about what they do. My hope is that governments and those that fund Science realise this asset and invest in these extraordinarily talented scientists and in the resources required for them to work in Latin America, not only to migrate other parts of the world. But even in the latter case, Latin America is, and I have no doubt that it will continue to be, an incubator for some of the best scientists in the world.

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Fig 1. Claudio Stern aged around 11, studying insects in the garden (Atlántida, Uruguay, c. 1965).

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To the Central Universities Council on Admissions

This is to Certify that:

In the Certificate of Proficiency in English Examination
the Candidate named below gained the result shown :

CLAUDIO STERN

Result in each test:

Oral Tests	5 good
English Language	2 fail
English Literature	3 pass
Translation from and into Spanish	3 pass

Result in Examination:

Failed in English Language only.
Allowed to re-enter/Ref. 1216/ June 1972 and December 1972

Place of Examination : Montevideo

Index Nr. : 8501-297

Date of Examination: December 1971

20th March, 1972

G.N.Bissett

Local Secretary
for Cambridge Examinations

GNB:ja

Fig. 2. Claudio's first attempt at the English test required for admission to a UK university in 1971: Fail in English Language.



Fig. 3. Cartoon of Claudio drawn by colleagues in the lab of José Roberto Sotelo at the Instituto de Ciencias Biológicas Clemente Estable (IIBCE) in Montevideo (c. 1975). Translation: "will they notice I am Uruguayan?" (the yellow/black symbol on the jacket is the coat of arms of "Peñarol", a major football club).



Fig. 4. Claudio receiving the Waddington medal from Matthew Freeman, President of the British Society for Developmental Biology, in 2006.



Figure 5. Signing the book, on Fellows' admission day to the Royal Society, 2008.



Figure 6. Claudio Stern (left) and Roger Keynes transplanting somites and neural tube while visiting Vicky Stirling's lab at the National Institute for Medical Research, Mill Hill, London in 1987.