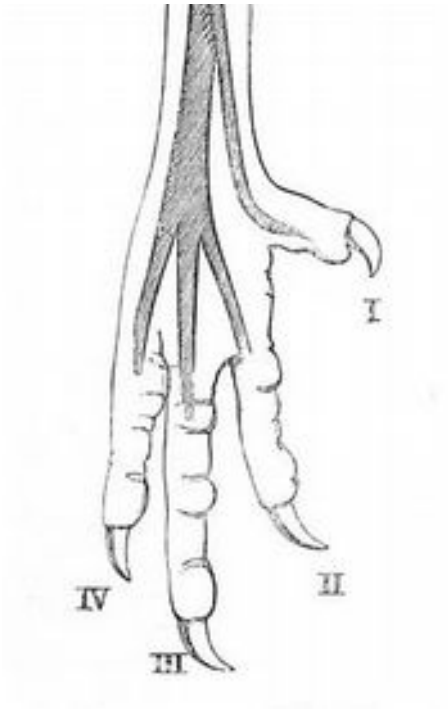
Megan, the ghost hunter.

One of the traditions of a British winter solstice is the telling of ghost stories. People gather in a darkened room to hear words softly spoken by a fireside's glow, listening hard to pick them out over the background noise of wild wind and of sleet impacting on the window panes. The best ghost story I heard this year – or possibly ever – was one delivered the day before the solstice, not at a cosy fireside, but in a lecture theatre in Guy's Hospital medical school as part of the winter 2016 meeting of the Anatomical Society. The remarkable thing about this tale is that it happens to be true.

These Anatomical Society research meetings are always fascinating – it is astounding how much about the structure of the human body we still do not understand – but for me this year there was an additional personal twist. I was invited to speak, and so were Prof Roger Keynes who co-supervised my PhD, and Dr Megan Davey who was the first person to work in my own laboratory when I set it up in 1995 and who has since been following a brilliant independent career. I was therefore especially interested to catch up with the work that these good friends and colleagues, to whom I owe such a massive debt of gratitude, have been doing. I'll tell Roger's story in a later blog: this one is about Megan, who has, in a way, become a professional ghost hunter. And, unlike run-of-the-mill 'ghost hunters' who are charlatans using use pseudoscience to hunt boring old ghosts of headless horsemen and the like, Megan applies *real* science to chicken eggs, and by doing so has uncovered the ghosts of dinosaurs.

The story begins, prosaically enough, with chicken feet. Anyone who has looked at the feet of an ordinary chicken, or almost any other bird for that matter, will have noticed that it has four toes: the 5th digit (our little toe) is missing. Birds evolved from Archosaurian reptiles, as did crocodiles, which have the five toes that we do. During the long evolutionary road from basal archosaurs to feathered therapod dinosaurs to dromaeosaurids to primitive birds, fossil skeletons show gradual diminution of the little toe until it disappeared. The evolutionary trend is obvious, but the mechanism has always been mysterious.

	
A chicken foot with the four digits (Image credit: WA Forbes, public domain, Wikimedia Commons)	Crocodile foot with five digits (Eric Kilby, CC-BY-SA-2.0, Wikimedia commons)

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In the development of the hand and foot of birds or of us mammals, the position of fingers and toes is determined by a complex interplay of signalling molecules, such as FGF8 from the very end of the limb, and Shh from the posterior (little finger/toe) side. An interplay of signalling events sets up a pattern of five areas that switch on genes such as Sox9 that mark cells that will become the bones of fingers or toes. Looking very carefully at the expression of Sox9 in the developing foot of a chicken embryo, Megan saw the expected four strong bands where the chicken's four toes would form, but she also noticed a very faint trace beyond. Careful measurement of the position of this

trace showed it to be just where mathematical modelling would suggest the fifth toe should be, if birds had one. Could this be the ghost of the little toe possessed by birds' distant dinosaur ancestors? And, if so, why does it not mature as the other toes do. Again looking carefully at the sites of gene expression, she found that the FGF8-producing zone at the end of a chick's limb is more restricted than it is in mouse, failing to wrap round towards the little toe side. Could this be why the fifth toe fails to thrive? To test the idea, she soaked some protein-absorbing beads in FGF8 and placed one of these beads further around the foot, effectively to extend the FGF8-producing region around the limb as far as it extends in mouse. The result was dramatic: some embryos produced an extension of a metatarsal (similar in appearance to the 'dew claw' on the foot of *Tyrannosaurus rex*) while a few few produced a 2-bone-long 5th digit like that of a primitive dinosaur.

It seems, then, that the developing foot region of a chick embryo contains within it a ghost of times past, a dinosaur foot capable of developing if only it is given an appropriate source of FGF8. Presumably, then, the evolution of birds feet was driven by a gradual change in the domain of FGF8 expression. How this happened is still a mystery, but the presence of the spectral (Sox9-positive) extra toe cells in the very early chick limb bud might be an ideal system for researchers to explore the molecular mechanisms that accounted for a major evolutionary event.

This was the best solstice ghost story I have heard in a long time.

Jamie Davies,
Edinburgh,
Dec 2016

LINKS:

Megan Davey's home page: http://www.roslin.ed.ac.uk/megan-davey/

A *Times* article about other aspects of her work: http://www.thetimes.co.uk/tto/news/uk/scotland/article4224139.ece