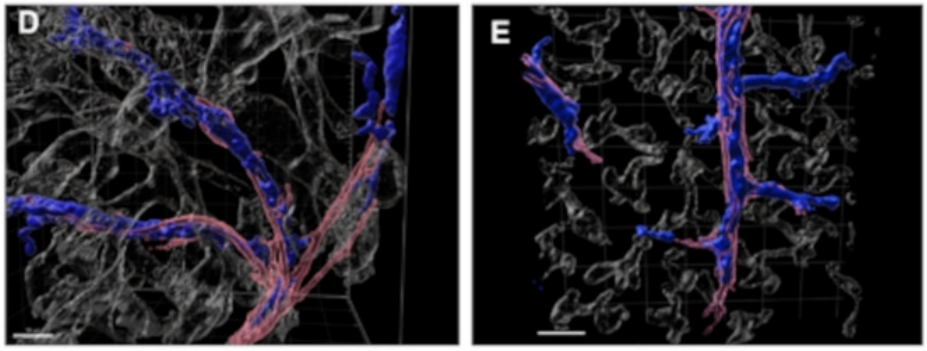
Watching kidneys getting nervous

The internal anatomy of kidneys is dominated by tubes – about a million urine-carrying pipes and blood vessels, running in an intimate and precise entanglement that is important to the way they function. Between these tubes are some other cell types, and these include neurons and their processes (axons). In adult kidneys, neurons tend to follow blood vessels. There are no doubt excellent functional reasons for this, given that the nervous system plays a part in controlling renal blood flow. But, to developmental biologists, the association looks intriguing for a different reason.

In a variety of other tissues, neurons and their processes arrive before blood vessels, and seem to tell the blood vessels where to be. This is true both in obviously 'neural' tissues such as the spinal cord, and in other parts of the body such as the developing limb. A series of papers going back to the 1970s have shown neurons to be present in the developing kidney from almost its earliest stages. Julia, who had already been working on formation of renal blood vessels (see 'Julia's Eggsperiments'), became interested in the question of whether blood vessels grow into the kidney along pathways already laid down by neurons.

Two images of neuronal processes, here stained red, growing alongside small arteries, here stained blue. These are images from Julia's paper, and come from kidneys of different ages.	

A central tenet for testing a hypothesis in science is that one tries to disprove the hypothesis. If any hypothesis survives many different attempts to disprove it, people begin to accept it as probably true. Science is done this way because a good experiment can disprove a wrong idea with absolute certainty, but it can never prove a right one as there is always the possibility of other theories, ones you have perhaps never thought of, also being compatible with all the observations you have made. Karl Popper set all of this out in his Conjecture and Refutation many decades ago.

One way of trying to disprove the hypothesis that neurons guide vessels is simply to look at when each arrives. If neurons guide vessels, they must be there first, before vessels arrive. If vessels arrive before neurons, then neurons cannot be guiding them. Julia therefore by staining examining kidneys of different developmental ages for neuronal cells and for blood vessels, using a variety of immunostains that could also give information on how mature blood vessels were.

Her staining showed that the blood vessels came first, and even that the muscle layers of maturing, larger blood vessels such as arterioles, also arrived before the neurons. The neurons never extended beyond the muscle-bearing parts of these blood vessels, in the sense that they never extended into the smaller and less mature parts. They just arrived next to a blood vessel just after muscle cells formed in the vessel walls. This observation was itself enough to disprove the hypothesis that neurons guide vessels in the kidney, or even that they guide the arrival of the muscle cells to vessels as the vessels mature. They cannot do either of these things: they arrive too late. Julia went on the the paper to establish a few other things, such as associations between neural processes and a subset of renal glomeruli, and the arrival of neurons even in cultured kidneys. But the main point was probably that the story established in other places, such as limb bud, of neural processes guiding vessels does not apply in kidney. That's one of the frustrating things about biology: there are so few real universal rules, and even if a pattern seems to be established, it is always necessary to check that it applies in every new situation.

Julia's work on this question is described in a short paper in *Biology Open*, an open-access journal run by the Company of Biologists (see 'links').

Jamie Davies, Edinburgh, September 2023

Links:

Julia's paper: Tarnick J, Elhendawi M, Holland I, Chang Z, Davies JA. Innervation of the developing kidney in vivo and in vitro. Biol Open. 2023 Aug 15;12(8):bio060001. doi: 10.1242/bio.060001. Epub 2023 Jul 31. PMID: 37439314; PMCID: PMC10411870.