100 YEARS AGO

A bicycle ride will be none the less enjoyable if you train yourself, not merely to travel far, but to take an interest in the sights and scenes through which you pass. For the sake of example, let me remind you that no country is so rich as England in the architecture of its village churches. It is no hard matter to learn to recognise the principal peculiarities of the architectural types which prevailed from the days of the Saxons to Sir Christopher Wren. ... But as soon as the elements of English church architecture are known, an old church ceases to be merely a picturesque object. It is an historical document which you yourself can read. You do not need the aid of the sexton to tell you which is the oldest part. You can make a good guess at when that aisle was added, or that window knocked in a wall obviously older than itself. A visit to a cathedral becomes an intellectual pleasure. Weariness at the drone of the verger as he recites his oft-repeated lesson is replaced by an alert desire to know if the authorities from whom he learnt it confirm or correct the rapid conclusions as to date or history to which you yourself have come.

From *Nature* 19 October 1899.

50 YEARS AGO

In a recent investigation, I have even demonstrated, among other matters, the existence of red blood corpuscle remnants in ancient Swedish skeletons (Viking age), buried without the embalming procedures used in Egypt and elsewhere. Pictures of relatively well-preserved organic framework of bone tissue were obtained with material even from so early a period as the Upper Stone Age. Various substances have been identified in mummified tissues by means of chemical methods. ... It was now thought possible to ascertain ... whether histamine occurs in measurable amounts in mummy tissue and other ancient human remains. Soft tissue (skin from the neck) and bone (cervical vertebra) from a mummy of the Egyptian Museum in Stockholm and supposed to be about three thousand years old were ground to a fine powder. ... A definite spasmogenic activity was found in the extract thus prepared. The spasm of the isolated guinea pig's small intestine elicited with the extract could be prevented with an antihistamine drug and was to a certain degree counteracted by atropine.

From *Nature* 22 October 1949.

ways. First, if axons go astray, this mechanism might help to eliminate them quickly, before they interfere with the orderly pioneering and assortment of axon tracts. Second, it could prevent axons reaching the wrong final target, where they might otherwise be incorporated in aberrant neural circuits[1]. Third, it opens the possibility of a combinatorial mechanism, where a limited number of factors derived from the intermediate or final targets could be used in different combinations to specify many distinct connections.

Wang and Tessier-Lavigne's work adds a fascinating new dimension to the increasing recognition that neurotrophic effects may go beyond the simple model of support by final targets. During development, the responsiveness of some neurons to different neurotrophins switches. Although this has not been tied unequivocally to intermediate targets, neurotrophins may contribute support at cell bodies or along pathways, while axons are still on the way to their targets[5]. There is also some analogy in later events, when motor neurons require support both from their muscle target and from the Schwann cells that wrap around their axons after reaching the target[3]. We also have several new questions. What is the precise developmental significance of the floor plate activity detected *in vitro*? Could the work have therapeutic implications in spinal-cord regeneration? What molecules are responsible for the activity? We don't have all the answers yet — but after all, life's a journey. ■

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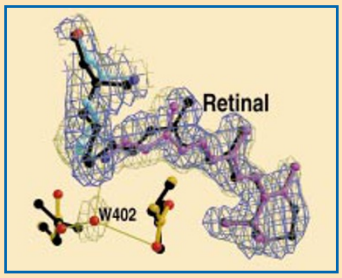
Protein crystallography

Frozen in time

Biochemical reactions are extremely rapid, but the methods for imaging the enzymes that catalyse them can take hours. To get round this problem, structures can be determined at temperatures around 100 K, literally freezing an enzyme's movements and allowing the intermediates in its reaction cycle to be observed. This has been done for bacteriorhodopsin in studies reported by Edman *et al.* in this issue (*Nature* 401, 822–826; 1999) and Genick *et al.* (*Science* 286, 255–260; 1999).

Bacteriorhodopsin is a pump that uses light energy to drive protons across bacterial purple membranes. A cycle of structural changes is triggered when absorption of a photon of light causes isomerization of bacteriorhodopsin's bound chromophore, retinal (purple in the figure). Intermediates in this photocycle can accumulate in crystals at low temperatures (see *Nature* 392, 206–209; 1998) or in mutant proteins, as used by Genick *et al.*, but subtler techniques are needed to trap the earliest and most elusive intermediates.



R. NEUTZE

Edman *et al.* maintained bacteriorhodopsin crystals in the dark, bathed in liquid nitrogen (110 K). They then drove the initial step in the protein's photocycle by illuminating the crystals with green light through an optical fibre (at a wavelength of 532 nm), and exposed them to a powerful synchrotron source to aid the rapid collection of data. The authors found that, despite the isomerization of a double bond, there is very little change in the overall shape of the retinal — in the figure, electron density after illumination (blue) is compared with that before (brown).

But there are other changes. The biggest of these is the escape of a water molecule (designated W402) from the vicinity of the retinal. This molecule previously formed part of a network of water and amino-acid residues connecting retinal to the outside of the bacterial membrane. Its loss triggers changes in this network, eventually resulting in expulsion of a proton from the bacterial cell.

One snap-shot cannot reveal the whole picture of how the bacteriorhodopsin pump works. However, by building up series of freeze-frame structures for all the intermediates in the enzyme's working cycle the mechanics of this, and other, molecular machines is being revealed.

Christopher Surridge