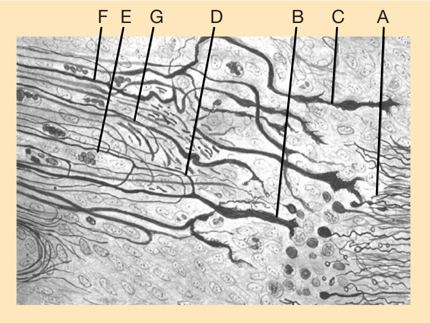

Figure 2 **Picture from Ramón y Cajal (1928)[2]. Interrupted dorsal root axons sprout (D–F) and form growth cones (B,C) but cannot enter the spinal cord (A). Ramer *et al.*[1] have now shown, however, that regenerating dorsal root fibres grow through the DREZ into the spinal cord under the influence of specific neurotrophic factors.**

has been known for about a hundred years[2]. Indeed, it has been studied as a model for the fact that nerve fibres can successfully regenerate in all parts of the peripheral nervous system, but not in the microenvironment of the spinal cord or brain (Fig. 2).

Several hypotheses have been proposed to explain this block to regeneration in the spinal cord and brain. These include the specific growth-promoting properties of peripheral-nerve glial cells (Schwann cells), as well as stop signals and growth-inhibitory cues associated with components of the CNS (in particular, the astrocytes of the DREZ and myelin-associated inhibitory molecules of the spinal white matter[3,4]). In fact, by directly implanting dorsal roots into the grey matter (neuronal regions) of the dorsal horn of the spinal cord, or by bridging the DREZ, some growth of sensory fibres into the spinal cord has been seen[5].

Ramer *et al.*[1] have now used a panel of neurotrophic factors to stimulate the regeneration of damaged sensory fibres. Surprisingly, these fibres overcome the inhibitory influences of the DREZ: they grow into the spinal cord and form branches in specific parts of the dorsal horn, their normal target area (see Fig. 1 on page 313).

Neurotrophic factors have many complex effects on responsive nerve cells, depending on the age of the neurons and the context in which the factors are presented. For example, developing dorsal root ganglion neurons with different functions (such as stretch receptors, touch-sensitive neurons, temperature sensors or pain sensors) respond to, and depend on, particular neurotrophic factors, especially those belonging to the neurotrophin family — nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4). Neurotrophic factors can also enhance the growth of fibres during development, in culture, and even within the CNS after damage to adult CNS fibre tracts[3,6,7]. In addition, they can reprogramme the response of neuritic growth cones to, say, repulsive or inhibitory factors[8].

Ramer *et al.*[1] infused rat brain with NGF, BDNF, NT-3 or glial-cell-line-derived neurotrophic factor (GDNF), and saw that interrupted axons grew through the DREZ into the spinal cord and its dorsal horn. However, the different growth factors had unequal effects — whereas GDNF had a strong growth-enhancing effect for different types of sensory axons, NT-3 affected mainly the large-calibre mechanoreceptors, and small-calibre pain and temperature fibres responded mainly to NGF. This specificity is in line with the developmental effects of these factors and the distribution of the corresponding receptors.

The next question is whether, when damaged nerve fibres regrow in the adult nervous system, they can find their targets and establish functionally meaningful connections. Little information is available in the CNS, although some behavioural improvements have been observed in studies of experimentally induced regeneration after damage to the spinal cord. This suggests that the mechanisms for target recognition and stabilization of functionally meaningful connections should be present[7,9,10].

Ramer and colleagues searched for evoked electrical activity in postsynaptic cells of the dorsal horn of their neurotrophin-treated, dorsal-root-lesioned animals. They found clear evidence for functional re-innervation of these spinal neurons by the regenerating fibres — the modality- and fibre-type-specific innervation profile of the dorsal horn was restored. The authors then tested functional reconnection by two behavioural reflexes: the protective (withdrawal) responses to pressure and to water at 49 °C applied to the forepaw. Damage to the dorsal root shifted the withdrawal responses greatly in both tests, indicating that the rats could not register the disturbing or painful stimuli. But recovery of both responses was seen within 2–3 weeks in the GDNF- and NGF-treated animals. Both of these neurotrophic factors influence pain- and temperature-sensitive neurons. So these results show that regenerating axons have contacted postsynaptic target neurons in the spinal cord in a functionally correct manner.

The factors and mechanisms that prevent or enhance the regeneration of damaged adult peripheral and central axons are now rapidly being unravelled. The demonstration that regrowing fibres can recognize target areas and form functionally meaningful connections (meaningful on the level of behaviour and the organism) is an encouraging step. Target-recognition signals may, in fact, be expressed throughout life in circuits that retain some structural plasticity. Strengthening of functionally meaningful synaptic connections (and retraction of

NATURE

100 YEARS AGO

Is New Zealand a Zoological Region?

Will you allow me to make one remark on the letter of Mr. H. Farquhar, advocating an affirmative answer to the above question. It is this: Throughout the whole argument there is an assumption which vitiates it, namely, that the amount of resemblance of the New Zealand fauna to that of *Australia* is what alone determines its resemblance to that of the *Australian Region*. Apparently, Mr. Farquhar does not believe that New Caledonia and the New Hebrides belong to the Australian Region, otherwise he would not adduce the fact of the land-shells of New Zealand being related to those of the above-named islands as an argument in his favour; and if these are omitted, then must New Guinea be also omitted. And if Australia by itself is to become a "Zoological Region," New Guinea and its surrounding islands must be also a "Region," the Central Pacific Islands another, and the Sandwich Islands yet another! This indicates the difficulties that arise if the Australian Region, as originally defined by Dr. Sclater and myself — and which I still hold to be far more natural than any subdivision can make it — be rejected.

Alfred R. Wallace.

From *Nature* 18 January 1900.

50 YEARS AGO

A new insect-proof packaging material which is cheap and very easy to handle has been developed by the Pest Infestation Laboratory of the Department of Scientific and Industrial Research. There is considerable wastage in packaged foods, resulting from the penetration of insects from outside. It was found that a layer of sand-paper formed an effective barrier, but did not prove practicable in use. Paper and corrugated cardboard impregnated with D.D.T. were unsuccessful because the insects bored straight through and so did not remain long enough in contact with the insecticide to pick up a lethal dose. The final solution was to use cellulose wadding, several layers thick, impregnated with D.D.T. When faced with this material the insect, after getting through the first layer, wanders in all directions and so takes up enough D.D.T. to be killed. Not one insect has ever got through this material in the course of numerous laboratory tests.

From *Nature* 21 January 1950.