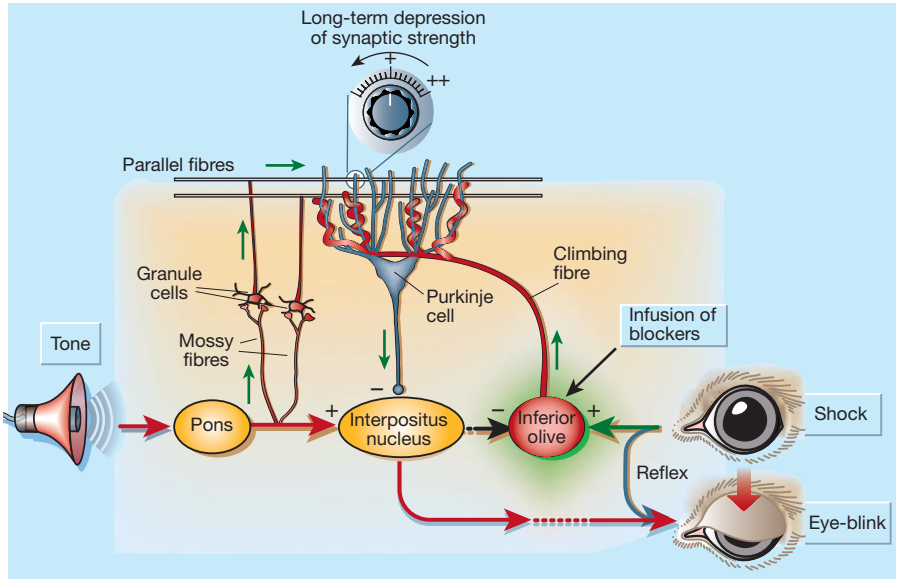

Figure 1 **Brain circuitry involved in acquisition and extinction of pavlovian eye-blink responses, studied in rabbits. An electric shock near the eye elicits a reflex action — a blink (blue arrow). After repeated pairing of a brief tone and a shock, the tone alone elicits a 'conditioned' blinking response, via the brain's interpositus nucleus (red arrows). Acquisition of this response (green arrows) is promoted by the joint activation of climbing fibres (by the shock) and parallel fibres (by the tone), inducing long-term depression[4] at synapses between parallel fibres and the Purkinje cells that usually inhibit the interpositus nucleus. This reduces the activity of the Purkinje cells and so reduces inhibition of the interpositus nucleus. Conditioned blinking fades away with repeated tone-alone trials. Medina *et al.*[1] show that infusion of picrotoxin (green 'halo'), which blocks the inhibitory neurotransmitter GABA, to the inferior olive prevents extinction. So, inhibition of the inferior olive and hence the climbing fibres drives extinction. In a normal situation, this probably occurs through the GABA-mediated connection between the interpositus nucleus and inferior olive (black arrow)[4,5,8,9].**

hence of climbing fibres arising from the inferior olive, is the signal for extinction.

How are the climbing fibres inhibited, causing extinction, under normal circumstances? Medina *et al.*[1] propose a role for the learned output of conditioning — the increased activity of the interpositus nucleus. This increased activity leads to conditioned eye blinking, but might at the same time generate inhibitory signals. This is not a new idea in itself[5,6]; it has already been proposed that outputs from the interpositus nucleus inhibit the inferior olive, and dampen the shock-induced excitation of climbing fibres[5,6]. This would explain the observation that the activity of the inferior olive diminishes as the conditioned eye response is learned[4–6]. Medina *et al.*[1] now show in computer simulations that such feedback inhibition actively drives extinction the instant the tone is given without the shock, that is, as soon as the inhibitory input from the interpositus nucleus is not competing with the excitatory signals from the shock. It is as if the animal is preparing for unlearning even as it learns.

What are the molecular mechanisms that underlie extinction? Long-term potentiation[4,7] (strengthening) of synapses between parallel fibres and Purkinje cells is one possibility. But this would not 'undo' the long-term depression at these synapses at the molecular level, because long-term potentiation is thought to affect presynaptic terminals of the parallel fibres[4,8] whereas long-term depression is expressed in postsynaptic dendrites (extensions) of the Purkinje cells[4,8]. If extinction does not counteract long-term depression at the molecular level, that might explain why relearning after extinction is faster than the original learning — because the original long-term depression has not been undone. To resolve this question, mutant mice that show normal acquisition but impaired extinction of the blinking response would be valuable.

Medina *et al.*'s work[1] also has broader implications. Climbing fibres are thought to be used more generally when learning movements, to convey to the cerebellum that errors are being made[4]. In the case of conditioned blinking, the signal for extinction (the inhibition of climbing fibres) might be interpreted as telling the cerebellum about a movement error — that is, the eye is blinking unnecessarily. One benefit of using the output from the interpositus nucleus to generate the extinction signal would be to save time in calculating this movement error. The error signal would begin before the eye actually blinks, if neuronal projections from the interpositus nucleus do indeed inhibit the inferior olive[4,5,8,9]. If the outputs from other cerebellar nuclei are used in the same way in calculating movement errors, then errors might be predicted before they are made, as

100 YEARS AGO

The similarity between malignant disease and tuberculosis has led numerous investigators to seek for an organism which would bear the same causative relation to cancer as the tubercle bacillus does to tuberculosis… The main point of difference between the adherents of the parasitic theory of the origin of cancer and their opponents centres upon the significance of certain undoubted microscopic appearances, chiefly of the growing portions, of cancerous growths. Some observers maintain that these microscopical appearances represent an organism of a protozoic type, others regard them as due to degeneration of the cancer cells. The majority, however, of microscopists do not regard the presence of a parasite in cancerous growths as proved. In the case of sarcomata, the parasite is supposed to be, not of animal, but of vegetable origin… If we turn from the study of the hypothetical cancer parasite to a consideration of the influence of general climatic conditions upon the incidence of cancer, we shall be treading upon more certain ground. The existence of so-called "cancer houses" seems to rest upon very strong evidence.
From *Nature* 20 March 1902.

50 YEARS AGO

Sir Lawrence Bragg delivered the thirty-sixth (1952) Guthrie Lecture of the Physical Society on March 12, when he discussed "X-ray Analysis of Proteins". Sir Lawrence said that the attempt to discover the atomic arrangement in the protein molecule seems very ambitious. Ever since Bernal first showed that crystals of protein give X-ray diffraction pictures, it has been clear that a protein molecule of a given type is a structure with a definite individual form; the X-ray diffraction spots are very sharp and reproducible and extend to regions corresponding to interatomic distances. The molecules are, however, of great complexity. It has been a triumph of X-ray analysis to pass from simple substances like rock-salt to such molecules as strychnine or penicillin with about one hundred atoms. Attempts are now being made to analyse a molecule such as haemoglobin, which contains fifteen thousand atoms. The reward, if an analysis were completed, would be great, because the determination of any one protein would undoubtedly cast a flood of light on the character of these bodies, which Nature has selected as the basis of living matter.
From *Nature* 22 March 1952.