This series of experiments builds on a foundation of studies dating back to the 1960s, when Pattison and Millson established the widespread extraneural distribution of infectivity in scrapie-affected sheep and goats. The chief architects during the 1970s were Hadow and Ecklund, followed, in the 1980s, by Fraser and Dickinson, and by Kimberlin and Walker. The importance of their contributions cannot be overemphasized in an era in which the power of molecular biology and accelerated publication has created a misguided tendency to neglect as already dated any research completed more than a few years earlier.

Thanks to them, and subsequent researchers (Kuroda, Diringer, Kitamoto and Lasmézas), we already know a good deal about the pathogenesis of transmissible spongiform encephalopathies. After introduction of the scrapie agent into various peripheral sites, including the stomach, infectivity first appears in the lymphoreticular system — tonsils, thymus, lymph nodes, and especially in spleen, in which a primary phase of replication occurs in B-cell-rich tissue fractions. Infectivity in these and other widely separated body organs implies that the infectious agent travels through the bloodstream, and this has been explicitly shown by isolation of infectivity from blood during both the pre-clinical and clinical stages of disease. Only after establishment of infectivity in peripheral organs does infectivity (and PrP) become detectable in the central nervous system; first in the spinal cord, and then in the lumbar and cervical cord segments and brain stem. Finally, genetically immunodeficient mice can partially resist intraperitoneal infection, yet they recover almost full susceptibility if immunologically reconstituted by the intraperitoneal injection of normal spleen cells.

This essential schema of scrapie pathogenesis is equally valid whether the infectious agent is a peculiar little virus or (as the Swedish Academy has just authorized) the prion protein. The observation by Klein *et al.*¹, that mature B lymphocytes participate in neuroinvasion, should lead to an increasingly precise appreciation of the molecular basis of scrapie pathogenesis. For example, do B lymphocytes act as blood-borne carriers of the infectious agent, or do they act while in the spleen? Serial-infectivity measurements of blood lymphocytes and spleen during the incubation period could be compared in normal and B-cell-deficient mice. Blood infectivity could also be evaluated in splenectomized B-cell- and T-cell-deficient mice. What would happen after infection of a null mouse with PrP-expressing intracerebral and peripheral nerve implants, or intracerebral and splenic grafts? And could combinations of immunodeficient and PrP null mice strains be created?

Neuroinvasion may turn out to have a hierarchy of options. B lymphocytes contacting terminal nerve endings in the spleen could be the most efficient route; other lymphoid-tissue sites and transfer cells might be less efficient; and direct contact with nerve endings (short-circuiting the lymphoreticular system) least efficient of all. Physical transfer of the infectious agent from a lymphoid cell to a neuron might also require a ligand molecule — the mysterious 'protein X', for example. Among the candidates are two proteins with an affinity for PrP, which have been proposed as cell-membrane PrP receptors in this month's issue of *Nature Medicine*^{3,4}.

What about the public-health and therapeutic implications of a role for B lymphocytes in peripherally acquired disease? There is a convincing link between the 'new variant' of Creutzfeldt-Jakob disease (vCJD) and consumption of infectious tissues from cattle with bovine spongiform encephalopathy (BSE). Moreover, the infectious agents of scrapie and CJD can be isolated from blood or blood components. The involvement of B lymphocytes in neuroinvasiveness adds another reason to consider a step that will deplete white blood cells during the commercial processing of blood, to reduce the possibility of transmitting CJD through blood products.

The outlook for therapeutic benefits is more problematic. Because we have no pre-clinical test for infection, nor any epidemiological clues as to who is at risk of vCJD, preemptive elimination of B lymphocytes is out of the question. PrP has been found in the tonsils of patients with vCJD, but this has so far been investigated only in clinically ill patients. We have no idea when — or even whether — PrP might appear during the incubation phase of disease. Moreover, even if PrP is present during the incubation period, we know that neuroinvasion occurs well before neurological symptoms. We cannot imagine that entire populations would submit to tonsillar biopsies as a screening procedure for vCJD. Thus, for the moment, we had best not push the implications of the involvement of B lymphocytes in neuroinvasion too far from the realm of basic science. When we know precisely how B lymphocytes influence neuroinvasion, it may be possible to nullify their effect without resorting to wholesale elimination strategies. □

Paul Brown is in the Laboratory of CNS Studies, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Maryland 20892, USA.
e-mail: pwb@codon.nih.gov

1. Klein, M. A. *et al. Nature* **390**, 687–690 (1997).
2. Büeler, H. R. *et al. Nature* **356**, 577–582 (1992).
3. Martins, V. R. *et al. Nature Med.* **3**, 1376–1382 (1997).
4. Rieger, R., Edenhofer, F., Lasmézas, C. I. & Weiss, S. *Nature Med.* **3**, 1383–1388 (1997).

Daedalus

Music with everything

Music used to be a scarce luxury; but these days it is available all the time and everywhere. The children of the electronic age can hear it 24 hours a day. But some folk still agree with George Orwell, who said that the purpose of light music is to prevent you thinking. Those who enjoy their own thoughts often wish to be without it. Daedalus is now attacking the problem.

The most intrusive music is the stuff that company telephone switchboards play to you while they try to make your connection. You are forced to listen to this pestilent noise in order to tell when it stops. And it's no good retaliating by singing a few bars back when you are finally connected. Your hearer will simply be puzzled: he never hears the stuff himself. So Daedalus is devising a circuit that can distinguish between speech and music, so as to kill the latter.

He points out that the power spectrum of music has regular peaks at the intervals of the musical scale. It should be simple to detect this pattern, and use it to drive a muting switch. You could then wait for your call to be connected in blessed silence, but would still hear the recipient's voice when he came through. If he started to sing, however, or to accompany himself on the banjo, you would lose him: the circuit will cut out any sound with that tell-tale musical periodicity in its power spectrum.

The same principle could tame the radio. News and weather buffs could hear them whenever they came on, without being distracted by the noise between. But what music-haters want most of all is a device to kill music heard through the air — as from Muzak speakers and other people's radios. So far, Daedalus has only a partial answer. His Music Saboteur has a microphone, a music-detector and a processor. When it detects music in the ambient sound, it splits the whole incoming signal into several bands. Some are raised a fraction of a tone while others are lowered; some are advanced in time and others retarded. This mixture is then put out through a speaker as a local spoiling signal. The user hears the incoming sound and the spoiler together. Speech is slurred and roughened by this combination; but music is utterly wrecked. Its frequency and time-domain power spectra are smeared out; its 'catchiness', its hold on the attention, is almost completely lost. It becomes mere formless background noise — still there, alas, but far less annoying.

David Jones