DNA, infects non-dividing cells in a wide range of hosts and results in a persistent infection. The chief advantage of the amplicon vector is that cloning manipulations and construction of the viruses are relatively easy, due to the small size (5–10 kb) of the plasmid. However, until the recent development of helper-free packaging procedures for amplicon vectors (which unfortunately are not included in this compendium), the helper viruses that co-purify with the recombinant amplicon viruses are problematic, as pointed out in the section by Epstein and Lowenstein.

The authors of the HSV-1 protocols are frank about the limitations of the current HSV vector systems. Because HSV is an enveloped virus, too fragile to band on cesium chloride gradients, it cannot be concentrated to the degree that encapsulated viruses such as adenovirus can be. Moreover, nonspecific cytopathic effects of the defective vectors restrict the number of viral particles that can be used to infect neurons. In addition, recombination can occur during the amplicon packaging process, to yield wild-type HSV revertants that exacerbate the cytotoxicity of the virus preparations.

Recent improvements in defective HSV vectors have corrected some of the limitations listed above. The most widely-used defective vectors were based on HSV-1 tsK, with a temperature sensitive single-base mutation in the IE 3 gene. Revertants of this mutant commonly arose during the packaging procedure, allowing production of lytic virus. The development of efficient packaging systems using deletion mutants of HSV-1, as described by Federoff and co-workers in chapter 12 of the manual, greatly reduced the frequency of revertants. The chapter by Tomasec et al. on the use of tsK mutants as vectors seems somewhat dated, in this context.

If a viral vector is to have utility for gene therapy, cytopathic effects of the virus must not eclipse the effects of the transgene. Unfortunately in this regard, HSV-based replication-defective vectors have been reported to be toxic to neurons in vitro and in vivo. However, second- and third-generation genomic deletion vectors with deletions in multiple early genes, as described by DeLuca and Glorioso in chapter 15, are substantially less toxic than are their predecessors. Moreover, the achievement of both high titers of vector by concentration in sucrose gradients and a more favorable ratio of vector to helper (Federoff et al., chapter 12) has helped to minimize cytotoxicity of present-day defective HSV-1 amplicon vectors.

For neurodegenerative diseases, transfer to the CNS of genes encoding specific trophic factors or neurotransmitters that could prevent or take the place of damaged cells is likely to be of great therapeutic benefit. Ex vivo modalities, in which genetically altered cells are transplanted into the brain, have proved to be particularly useful for this form of gene therapy. Palmer and Gage note in the introduction to their outstanding set of protocols for grafting engineered cells into the central nervous system, that progenitor cell lines from the CNS or multipotent stem cells show great promise as vehicles for delivering the appropriate genes to the brain by ex vivo strategies.

The final section of the manual contains protocols for specific in vivo application of gene transfer methods. These include an excellent set of protocols by Hunter and co-authors on replication-competent viral therapy for CNS tumors. The protocols are set out in great detail and are accompanied by photographs of the surgical procedures that will greatly aid neophytes in these techniques. Also notable is the discussion by Wood et al. of the practical implications of the production of immune responses to viral vectors used in gene therapy. Whether a seasoned user of CNS gene transfer protocols or a gene transfer novice who is seeking to use 'genetic pharmacology' to answer basic neurobiological questions or treat disease, the reader of this volume will benefit from this practical guide to the latest techniques for delivering genes into the nervous system.

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The Cerebral Code
William H. Calvin (Editor). MIT Press, Cambridge, MA, 1996; ISBN 0-262-03241-4, £14.95 sterling.

With 'The Cerebral Code', William Calvin gives us a book that, in his words, is 'about thought, memory, creativity, consciousness, narrative, talking to oneself, and dreaming.' This kind of promissory note will surely tempt anyone interested in the brain to read further. The book follows a number of his previous popular accounts on brain function and evolution; however, Calvin changes pace with 'The Cerebral Code', and offers its contents first to his fellow scientists, and secondly to the

lay reader. Thus, the book makes free use of neuroscience and cognitive science jargon—these entry standards will probably diminish the number of readers that find the book accessible.

There are two main hypotheses on which most of the book is based. The first hypothesis is anatomical/physiological: intrinsic cortical axons come in a standard length (about 0.5 mm), and, through recurrent excitation, this wiring motif encourages the formation of hexgaonal patterns of synchronous neural activity. The second hypothesis is algorithmic: the hexgonal patterns are able to copy (clone) themselves to other parts of the cortex.

This cloning process is said to implement a full-fledged neural version of Darwinian evolution, whose products explain all of the interesting phenomena trumpeted above. The combination of these two ideas is said to yield a competition among hexagonal patterns of synchronous neural activity—in Calvin's words a 'hexgaonal cloning competition.' The ideas about standard length axons are not new, nor is the idea that the brain may operate on selective principles. The novel proposal of Calvin's is the claim that the 'hexagonal cloning competition' is the correct representational level for connecting the operation of the brain to the operation of memory, thought, metaphor, walking, throwing, and so on. Clear so far.

This effort by Calvin pokes right at the soft underbelly of modern neuroscience—a field badly in need of new ideas. Experimental techniques continue to evolve at a remarkable pace. We are now able to peer into thinking brains, measure calcium levels in single neurons in vivo, and dissect the function of isolated ionic channels. It is truly a remarkable time for experimental brain science; yet, we remain vastly ignorant of how to connect the functioning of brain parts to mental function—we are in need of concrete, testable theories.

The two main hypotheses arm Calvin with a 'mechanism': hexagonal patterns of neural activity compete to reproduce themselves in the superficial layers of the cerebral cortex. He spends the first 100 pages of the book introducing the mechanism, and drawing analogies between it and the evolution of species in complex environments. Another important lesson that the reader learns in these first 100 pages is the degree to which Calvin will leave the details unspecified.

We are told that the 'hexagonal cloning competition' is analogous to evolving species of complex organisms; however, the details of this connection are never stated. Also missing are critical details about why cloning occurs, how it is controlled, why a competition among patterns ensues, and so on. The reader is told that these events would occur, but not enough about why they would occur. In short, the details are woefully underspecified and simply do not allow one to judge the adequacy of the ideas. This same kind of complaint also arises when one tries to understand the way in which the competing species metaphor accounts for things like memory, creativity, and consciousness.

No matter how provocative one may find Calvin's suggestions, his 'Darwin machine' is constructed primarily by assertion and not by demonstration. It is unfortunate that he did not try to implement some version of his ideas on a computer. The counter to these complaints could be that this is more a popular book, more like an essay; however, the author declares in the prolog that the book is primarily for fellow scientists. This declaration lays down a different set of standards against which the book is judged, and these standards do not mistake assertions for explanation.

The last 100 pages of the book uses the hexagonal cloning idea to account for almost every mental phenomenon that ever drew an interested student into the study of psychology or cognitive science—memory, category formation, language acquisition, and consciousness—just to name a few. Actually, by page 177, much of the work is through—'If the reader will indulge me in another celebratory recapitulation, I'll run through a selection of the theory's predictions, together with some related descriptive successes.' There is clearly a large discrepancy between what Calvin feels that he has explained and what actually shows up explained on the written page. Either I missed the most critical profound points or they simply were not there. Many of Calvin's previous books have been enjoyable, clear accounts with ample references; therefore, I find puzzling the current entry in his publication list.

As stated earlier, neuroscience needs new ideas—even wrong ones. This means that we must allow speculation in some proportion, however, when the number of hypothetical details is about the same as the number of phenomena explained, the speculation is not constructive. There are numerous books out that speculate widely on the mind–brain connection, yet the authors feel a real obligation to show clearly the data and arguments on which they base their speculation. One excellent recent example is Daniel Schacter's book on memory (Searching for Memory: The Brain, the Mind, and the Past, Basic Books, 1996) which is filled with interesting anecdotal accounts presented alongside detailed summaries of many decades of both psychological and neurobiological research. 'The Cerebral Code' may have offered an answer to many profound scientific puzzles, however, the answer appears to remain encrypted.

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