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Poumay raises an important issue related to Web publishing and archivability. His solution to the perceived impermanence of Web material, however, would hamper the evolution of Web science publishing. As a publisher of a Web scientific journal, *Optics Express* (www.osa.org), I think there is room for several approaches to the archiving of Web information. For example, material can be stored indefinitely on servers or duplicated on "mirror" sites elsewhere, or copies can be made and stored in other media.

What is important is that the publishing organization be fully committed, financially and organizationally, to this enterprise—a major change in direction for most publishers and for-profit organizations. That leaves scientific societies and associations, which are beginning to take steps to ensure that such a change takes place.

To suggest, as Poumay does, that only articles that have equivalents in print should be cited is not practical and slights fully reviewed and archived electronic journals.

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Investment in Tokamak Fusion

The debate over the future of the International Thermonuclear Experimental Reactor (ITER) (J. Glanz, "Requiem for a heavyweight at meeting on fusion reactors," News & Comment, 8 May, p. 818), unfortunately, does not go far enough. The real issue is not how much money should be invested in the next large tokamak, but whether any further investment in tokamak confinement is warranted at this time.

The tokamak has been the main approach to magnetic confinement fusion since its inception almost 50 years ago. During the intervening half century, great progress has been made in understanding the physics of toroidal confinement and in translating that understanding into improvements and innovations in tokamak design. Although tokamak design is still based on empirical scaling laws, confidence in these laws has been strengthened by a wealth of experimental data. Numerous reviews of the ITER design have concluded that if the machine is built to the ITER design specifications, there is little doubt that it can achieve its scientific goal of a sustained thermonuclear burn.

This statement reflects both the triumph and the tragedy of fusion research, because it also implies that if a tokamak is significantly smaller than the ITER design, it will not achieve a sustained thermonuclear burn and thus will not provide the basis for a power-producing reactor. The scientific community needs to reexamine the premise on which the public was originally asked to support fusion research, namely, that it would lead to the development of a practical, power-producing technology. In light of today's knowledge, it is highly unlikely that further development of the tokamak will lead to that outcome.

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Cerebellum and Learning: A Complex Problem

There is increasing experimental support for

the idea that the cerebellum has a special role in motor learning and, perhaps, the storage of motor memories (*1*, *2*). A consistent feature of many models of such cerebellar learning is that memories might be encoded by changes in efficacy of parallel fiber synapses on Purkinje cells, changes that might be governed by a teaching or reinforcing input through a climbing fiber from the inferior olive to each Purkinje cell. Such input might behave in a manner predicted in a formal model of classical conditioning (*3*), in which reinforcement value declines as learning proceeds. One of us suggested previously that nucleo-olivary inhibition (*4*) could serve to inhibit olivary input to the cerebellar cortex as learning occurs and so provide a mechanism for Kamin blocking (*5*) in cerebellar-dependent classical conditioning (*6*).

In their report "Inhibitory cerebello-olivary projections and blocking effect in classical conditioning" (23 Jan., p. 570), Jeansok J. Kim, David J. Krupa, and Richard F. Thompson state that their findings support both hypotheses. They analyzed olivary activity before and after classical conditioning of the rabbit eyeblink-nictitating membrane response (NMR), which is a cerebellar-dependent learning task. Cerebellar Purkinje-cell complex spikes (which are responses to climbing fiber input) were elicited by an air puff unconditional stimulus (US) before and after conditioning if the US was presented alone. Kim *et al.* found that, after conditioning, if a tone conditional stimulus (CS) preceded the US and a conditioned response (CR) was elicited, then complex spikes were absent at the onset of the US. In a second experiment, nucleo-olivary inhibition was antagonized with picrotoxin and Kamin blocking was prevented.

Although these findings appear to be consistent with the model outlined above, they can be disputed. The normal frequency of complex spikes is only 1 to 2 hertz and does not exceed about 10 hertz with normal sensory stimulation (*7*), although strong nociceptive input has been reported to cause firing frequencies up to 20 hertz for brief periods (*8*). The upper frequency limit is set by calcium conductances in the olivary membrane (*9*) and appears to be inviolate, but Kim *et al.* report observing much higher frequency "complex spikes," four in less than 100 milliseconds in single-cell recordings, as shown in figure 3 of their report. These high frequencies indicate that the recordings likely did not accurately discriminate between olivary complex spikes and parallel fiber-driven simple spikes. If the recordings were from multiple cells, then the problem of resolving complex and simple spikes is even greater. But even if these responses are complex spikes, the data still do not support the conclusions, because the "complex spikes" occur most frequently during the tone CS. This result is inconsistent with the olivary reinforcement model proposed by Kim *et al.*

An essential requirement for a test of this model is that the recordings are from the appropriate Purkinje cells. But the only criterion used in the report to select the relevant cells was that they responded to the air puff US. Because some of these cells also respond to the tone, it is unlikely that they were specifically involved in controlling eyeblink.

Because the electrophysiological evidence in support of olivary reinforcement is equivocal, more reliance must be placed on findings in the second experiment in the report. Kamin blocking was efficiently prevented by some picrotoxin injections close to the inferior olive. But with only single examples of an effective and an ineffective cannula injection, it is difficult to know whether these brainstem picrotoxin infusions specifically exerted their effects through disruption of olivary mechanisms.

Olivary input to the cerebellum as a reinforcer in this motor learning is an attractive hypothesis which, in our view, remains unproved.

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Response: The letter by Hesslow and Yeo centers on the olivary activity-induced complex spike recording in Purkinje neurons. With regard to the "complex spikes" of higher than normal frequency (which are present in figure 3 of our report), we agree that the normal frequency of complex spikes is relatively low, as was confirmed by the complex spikes that we recorded in rabbits under normal conditions (our figure 2). The procedure for single-unit recording was fully described in our report. Thus, the crucial question is, Should the frequency of complex spikes remain normal (or unaffected) when picrotoxin is infused into the olive?

Several immunocytochemistry studies with an antiserum to glutamate decarboxylase indicate that there is a dense concentration of boutons containing γ-amniobutyric acid (GABA) in the olive (*1*). Additional evidence indicates the existence of local circuit neurons (that contain GABA) in the olive—including in the dorsal accessory olive (*2*). Because GABA neurotransmission is considered to be primarily inhibitory (*3*), substantial removal of both externally and internally originated GABA inhibition of the olive may drastically alter the climbing-fiber–induced complex spike activity in Purkinje neurons. This possibility appears to be confirmed by the in vitro finding that modulation of membrane potential and of dendritic excitability alters the frequency of oscillation of olivary neurons (*4*). Also, the removal of GABA inhibition may increase the receptive field size of olivary neurons, analogous to effects seen in the primary somatosensory cortex (*5*), and this effect in awake animals may also contribute to increased firing rate. Finally, because the concentration gradient of picrotoxin is much higher inside the cannulae than in the surrounding brain tissue, it is possible that some drug diffused out of the cannulae before infusion, which also might have contributed to increases in complex-spike activity.

With regard to the blocking experiment in our report, although one would prefer to assess the extent of the drug spread in any local infusion drug study, at the time of our experiment a radioactively labeled picrotoxin was not available. In our study, however, only those cannulae located within or just adjacent to the dorsal accessory olive yielded effective results. Infusions of picrotoxin through cannulae located in surrounding regions did not prevent blocking.

In sum, as previously stated in our report, intra-olivary picrotoxin infusions seem to increase the overall frequency of complex spikes and block the learning-induced suppression of the olivary reinforcement activity (*6*). The latter observation and evidence from the blocking experiment are, in our view, consistent with the olivary reinforcement model of eyeblink conditioning (*6*, *7*).

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Progression to AIDS

M. Smith *et al. (1)* suggest that failure to observe an association between the chemokine receptor mutation *CCR2-64I* and delayed progression to AIDS or death in seroprevalent [HIV-1 (human immunodeficiency virus–1) seropositive at enrollment] cohorts (2) could be the result of imprecision in estimating the date of seroconversion, resulting in a masking of the protective effects of the genotype. We present evidence that biased exclusion of more rapid progressors to disease among seroprevalent cohorts would contribute to limited discrimination for such cohorts.

The Hemophilia Growth and Development Study (HGDS) has contributed data for studies of CCR2 conducted by the Laboratory of Genomic Diversity at the National Cancer Institute (NCI). The HGDS is a "seroprevalent" cohort, with most HIV+ participants (n = 207) exposed during a narrow window between 1982 and 1983. Participants were enrolled in the study in 1989 and 1990, a mean of 6.7 years after infection. In June 1992, centers began shipping fresh whole blood to NCI for the development of lymphoblastoid B-cell lines, the source of the DNA used to classify genotype. Cryopreserved cells were used to prepare cell lines for participants who had died or had dropped out of the study before June 1992. Cell lines were successfully developed for 90% of the cohort.

The characteristics of participants missing from an analysis are at least as important as those who are included (3). Missing a cell line occurred more frequently in the HIV+ than in the HIV– cohort (15% versus 2%), and missing a cell line was associated with increased severity of HIV disease. The median