β-cells tolerate this tissue and fail to respond to the MHC-antigen in MLR[8]. In none of these models would clonal deletion be expected to play the major role in developing tolerance, as the particular antigens involved are not expressed on haematopoietic elements within the thymus. Clonal anergy seems a possible mechanism, although immunoregulation or a suppression of autoreactivity could also be responsible.

The findings of Rammensee *et al.* have striking similarities to an *in vitro* murine model of T-cell unresponsiveness first described by Jenkins and Schwartz[9]. In this system, interleukin-2-driven proliferation by type I $CD4^+$ T-cell clones responding to peptide antigen and syngeneic splenic antigen-presenting cells (APC) is blocked if the APC population is pretreated with a chemical fixative. Rather than stimulating proliferation, these cells, in the presence of peptide antigen, induce the T cells into a state of proliferative unresponsiveness. This state of unresponsiveness appears to be entirely analogous to that seen in the $V_\beta 6^+$ population following treatment of the mice with Mls^{a+} spleen cells — T-cell receptor expression is intact, yet interleukin-2 production and proliferation cannot be induced in response to normal APC and antigen.

Comparisons to this *in vitro* model of unresponsiveness may provide clues to the mechanism of the induction of T-cell *Mls*-tolerance *in vivo*. Two points in particular are worth considering. First, the induction of unresponsiveness *in vitro* is dependent on the mobilization of intracellular calcium in response to T-cell receptor occupancy[10]. Second, an accessory cell-derived costimulatory signal, delivered at the time of the calcium flux, is capable of blocking the induction of unresponsiveness, and is also responsible for synergizing with signals generated via the T-cell receptor to induce the production of interleukin-2 and T-cell proliferation[11]. A failure to deliver this costimulatory signal during the $V_\beta 6^+$ T-cell response to the transferred Mls^{a+} spleen cells *in vivo* could be important for the induction of the tolerant state.

The Mls^a antigen appears to be expressed primarily on B cells[2]. Resting B cells represent a poor source of costimulatory signals, as judged by their poor ability to augment the proliferation of T cells responding to antigen presented by fixed APC[11], and by demonstrations of their poor stimulatory capacity in primary MLR despite reasonable expression of MHC molecules[12]. These cells are, however, capable of inducing a T-cell proliferative response to the Mls^a antigen *in vitro*. Costimulatory signals must certainly be provided by nearby splenic macrophages or dendritic cells to account for the strong proliferation in these cultures. The delivery of this second signal would also block the induction of unresponsiveness in the culture (*a* in the figure). The response seems to be different on recognition of the Mls^{a+} B cell *in vivo*. The development of the anergic state suggests that little costimulatory signal is delivered at the time of occupancy of T-cell receptors, and the effects of the calcium flux are dominant (*b* in the figure). Why these T cells fail to receive the second signal from neighbouring accessory cells (as would seem to be the case *in vitro*) is unclear. The ability of Batisto and Bloom[13] as well as Miller *et al.*[14] to induce tolerance to several antigens following the intravenous delivery of antigen-coupled or haptenated spleen cells suggests that the route of administration and presumably the tissue compartment within which the recognition of Mls^a occurs are critical variables.

The biochemical basis of proliferative unresponsiveness *in vitro*, namely increases in intracellular calcium concentration in the absence of a costimulatory signal, could also represent a common biochemical principle that underlies each of the models of T-cell tolerance. Mobilization of calcium in thymocytes undergoing negative selection seems to be the trigger that induces apoptosis and the deletion of these self-reactive clones[15]. The recent demonstration that $CD8^+$-suppressor T cells can induce clonal anergy in $CD4^+$ T cells responding to *Mycobacterium leprae* antigens *in vitro* suggests that suppressor T cells may operate by interfering with the delivery of a costimulatory signal to other antigen-stimulated T cells[16]. Such common themes may turn out to be important to our understanding of T-cell tolerance as the questions of deletion versus suppression versus anergy are answered. □

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DAEDALUS

Coca-coda

COCAINE addiction is a growing problem in many cities of the Western world. Daedalus now plans to counter it with a novel strategy based on a curious episode in nineteenth-century imperialism. In those innocent days, cocaine was a valued medical drug; and to capture the market for it, the Dutch tried to transplant coca plants from South America to their colonies in Indonesia. The plants grew quite well: but, bafflingly, yielded almost no cocaine.

What was going on? Daedalus reckons that the plants were infected by some wild plant virus from the local forests. Not all such viruses are deadly; some merely cause small metabolic changes. So Daedalus advocates an expedition to Indonesia to identify this virus, the plants it naturally infects, and the insects which spread it. These could then be covertly transported to South America, and released around the illicit coca plantations.

The results would be most intriguing. Modern *Erythroxylon coca* is a highly cultivated plant, bred over centuries to produce far more cocaine than is good for it. Freed from this pointless biochemical burden, the infected coca plantations would flourish as never before, but would enigmatically fail to yield any cocaine. Apoplectic drug barons and mafia bosses would suddenly find themselves making a loss on their investment. The surprise would be even greater if the virus turned out not to suppress alkaloid production, but switched it instead to some alternative alkaloid like strychnine. Once well entrenched in the local vegetation, the virus would be impossible to eradicate. All concerned would have to find another racket, or even (if all else failed) an honest trade.

This subtle principle can clearly be extended. Once identified, the plant virus might be mutated or genetically engineered to switch the alkaloid metabolism of other pharmacologically active plants. Suitable variants could subvert the opium poppy fields of Asia or the many illicit cannabis plantations around the world. Anti-smoking fanatics would love to release a nicotine-suppressing virus onto the world's tobacco fields. But Daedalus himself wants to challenge the hypocrisy of society's wine snobs with a virus that suppresses the alcohol synthesis of wine yeast, but leaves the complexities of fermentation otherwise untouched. The resulting wine will of course retain all the much vaunted subtleties of bouquet and palate that *bon viveurs* insist are the reason for their interest and devotion; but it will no longer make them drunk. The price which this new vintage commands, and the degree of dedication with which it is bought, laid down, argued and enthused about, compared with other vintages, and finally sampled, will be most revealing. David Jones