Natural painkillers

To the editor—Since the discovery of the ability of immune cells to produce pro-opiomelanocortin (POMC)-derived peptides, such as endorphins and corticotropin (ACTH)¹, questions concerning their structure and function have persisted. In a recent News & Views article in the August issue of *Nature Medicine*, Sharp and Yaksh addressed these issues with particular regard to endorphins². As reported, the elegant work of Christoph Stein and colleagues has now assigned at least one function—immune cell-derived endorphin can control pain by acting on sensory nerve terminals at sites of inflammation. It should also be mentioned that in addition to acting on classic targets such as nerve terminals, immune cell-derived endorphins can also function as regulators of immune cells themselves via opiate receptors³.

With regard to structure, Sharp and Yaksh pointed out the need for rigorous characterization of the peptides and the demonstration of POMC and its full

length transcript. Unbeknownst to them, such information was in press at the time and has now been published⁴. Specifically, using primer extension and RNase protection assays we have now demonstrated full-length POMC mRNA in rat mononuclear leukocytes which is upregulated by mitogen treatment and identical in sequence to that of the pituitary gland. For reasons we do not understand, we and others have been unable to demonstrate full-length POMC mRNA by polymerase chain reaction (PCR) techniques and this has led to the generally accepted notion that only truncated versions of the mRNA are present^{2,4}. Our most recent results show that this conclusion was wrong.

Consistent with the presence of full-length POMC mRNA, the 31kd POMC protein itself was observed by western blotting and was proteolytically processed in a way consistent with the pituitary gland⁴. While immune cell-derived endorphin has yet to be se-

quenced at the amino acid level, that of another POMC product, ACTH, has and it is identical to the pituitary peptide⁵. Considering this, and the presence of authentic, full-length POMC mRNA and its translation product in immune cells, it now seems that questions about the authenticity of immune cell-derived endorphin are academic ones at best.

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Effects of RU486 on HIV-1 replication

To the editor—In the October issue of *Nature Medicine*, Ayyavoo *et al.* reported that the anti-glucocorticoid/antiprogesterone drug RU486 could counter the effects of hydrocortisone-, dexamethasone- and Vpr-mediated T cell dysregulation in HIV-infected cells¹. This work was paid significant attention by the lay press that reported that drugs such as RU486 might have utility as anti-HIV agents. As we have generated data to the effect that RU486 can exert differential agonistic and antagonistic effects on HIV-1 replication in different cell types, we urge caution in regard to that interpretation.

In fact, it is well known that HIV-1 replication can be stimulated by exposure of infected cells to various glucocorticoid agonists^{2,3}. This effect is thought to be mediated through the cellular glucocorticoid receptor (GR), and to represent genuine transcriptional enhancement mediated by discrete functional glucocorticoid response elements located within the HIV-1 long terminal repeat (LTR) and intragenic viral sequences^{4,5}.

These findings may help to explain cases of rapid progression to AIDS in HIV-infected individuals undergoing therapy with prednisolone⁶ as well as the unusual incidence of pathological disorders of the pituitary-adrenal axis seen in AIDS patients⁷.

RU486 is prescribed as an abortifacient. HIV-infected women may elect to terminate pregnancies, both because of the risk of vertical transmission of infection and because of concerns about the effects of pregnancy on the course of HIV disease. Yet, no comprehensive study of the effects of RU486 on HIV replication has been undertaken. In this regard, we tested RU486 in the hope of establishing an inhibitory effect and a potential basis for the use of glucocorticoid antagonists in the treatment of HIV-associated disease.

On the basis of both reverse transcriptase (RT) and p24 ELISA assays that monitored levels of HIV released into culture fluids, we found that RU486 caused a dose-dependent increase in HIV-1 replication in acutely infected H9 human T lymphoblastoid cells, with a 7-fold in-

duction noted after 17 days in culture ($P < 0.001$). Peak levels of stimulation were seen at concentrations of 1 mM RU486, with extent and kinetics of the enhancement similar to those previously reported for cortisol and dexamethasone³. This suggests that stimulation of HIV-1 replication by these three compounds might occur by similar GR-mediated mechanisms. In sharp contrast, RU486 caused a dose-dependent inhibition of RT activity in HTLV-I-transformed MT-4 human lymphoid cells, at both three and seven days following infection with HIV ($P < 0.01$ on day 7). Differential effects on HIV replication could not be correlated with cytostatic effects of RU486, since uninfected cells showed no growth inhibition over seven days at concentrations up to 1 mM RU486, nor with differences in GR levels or Kd values for dexamethasone. This work was performed in order to establish whether RU486 could reproducibly inhibit HIV-1 replication in tissue culture systems. Instead, we found that RU486 caused differential stimulatory and inhibitory effects, depending on