done so to counter neutralizing antibodies in general, and those directed at its CD4-binding site in particular. These antibodies are highly prevalent in HIV-positive human serum[8]. The requirement of HIV-1 for protection against neutralization may be lost when the virus is grown in tissue culture and more rapidly growing strains are selected. Coincidentally or otherwise, such strains may be more sensitive to neutralization in general, and to neutralization by sCD4 in particular. The neutralization resistance of primary viruses might have dire consequences for the chances of successful therapeutic intervention by the administration of neutralizing antibodies.

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SIR — Nara *et al.*[1] noticed that in studies with chimaeric viruses, designed to map viral determinants for macrophage- and T-cell-line tropism, replication of all the variants in peripheral blood mononuclear cells (PBMC) was ignored. In fact it is well known that PBMC are the susceptible target cells for all variants of HIV-1[9–11]. Nara *et al.* suggest that "viral envelope elements that otherwise abolish infectivity in cell lines are tolerated in PBMC, suggesting fundamental differences of viral entry at the cellular level for these cells". It is the permissiveness of PBMC that they call 'enhanced permissivity' or 'universal tropism'. Rather than restrictive viral determinants, they now assume active cellular repression of the entry process.

Is this a matter of semantics or is it a real change in paradigm and, if so, what is to be gained? Apart from the fact that target cells hardly affect the neutralizing capacity of sCD4 (ref. 7), it is unclear how this concept of universal tropism contributes to the unravelling of the molecular mechanisms involved. Moreover, it has been demonstrated that also in PBMC differences in *env* gene-related biological properties exist, indicating that PBMC are not fundamentally different from other cell-types in this respect[2,9]. The prevailing interpretation is that monocytes and T-cell lines carry distinct secondary receptors that discriminate for monocytotropic and T-cell-line tropic isolates. The susceptibility of PBMC for all virus isolates therefore might be due to the expression of both these secondary receptors on each primary cell or to the expression of these receptors on different cells present in the mixture that constitutes the PBMC population. The fact that macrophage- and T-cell-line tropism can be reciprocally exchanged by *env* gene fragments suggests that this virus element can distinguish between the additional receptor on the surface of these two cell types[12,13]. This knowledge of the viral *env* gene-encoded interaction site(s) will aid in the identification of putative additional receptors. Moreover, for this purpose cell types that express distinct additional receptors are required rather than PBMC, which will not allow discrimination of possible receptors.

Although PBMC should be used in primary isolation studies to obtain the complete spectrum of virus isolates, we fail to see what the impact of the new concept of 'universal tropism' will be on strategies for unravelling cell tropism of HIV-1 variants.

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Neurotransmitter role for ATP?

SIR — It would be unfortunate if the idea that ATP is commonly a cotransmitter at cholinergic synapses[1] entered the textbooks, as there is so far no evidence for this at any cholinergic synapse. Neither the synapses studied in slices containing the habenula[2], nor those in cultured sympathetic coeliac ganglia[3] are cholinergic. All fast excitatory preganglionic synaptic events in neurons of intact guinea pig coeliac ganglia are rapidly and reversibly abolished by tubocurarine or hexamethonium[4], as in all autonomic ganglion cells studied so far. The lack of effect of the P_{2x} purinoceptor antagonist suramin at intact ganglionic synapses has recently been confirmed[5]. The purinergic 'autapses' which formed between cultured coeliac neurons[3] were presumably made by the terminals of those noradrenergic neurons[6] which normally end on blood vessels within the gastrointestinal tract. Blockade of vasoconstriction and of excitatory junction potentials in these arterial vessels by suramin[5] are taken to indicate that ATP is released from perivascular endings.

We are unaware of any direct evidence that ATP and acetylcholine are co-released from any one type of peripheral nerve terminal. Stimulation of the innervation of cholinergically innervated visceral organs such as the bladder may produce atropine-resistant responses which are blocked by purinoceptor antagonists[7], but there is no reason to conclude that these necessarily arise from cholinergic terminals. The neurochemistry of non-adrenergic postganglionic neurons innervating the bladder is diverse[8,9], and at least two types of non-adrenergic neuron may innervate the muscle[10]. As there is currently no marker to distinguish cholinergic from non-cholinergic neurons in the peripheral nervous system, the possibility that two sets of terminals are present cannot be excluded.

On the other hand, the results reported by Evans *et al.*[3] are unexpected. The abolition by cholinergic antagonists of fast excitatory synaptic events between cultured rat superior cervical ganglion cells[11] is the basis for our current understanding of the plasticity of sympathetic neurons in the transmitter phenotype they express under different environmental influences[12]. Whether the synapses that Evans *et al.* studied were made by the terminals of noradrenergic vasoconstrictor neurons which had retained their original purinergic properties, or whether the terminals had been converted to purinergic ones by environmental influences *in vitro*, remains to be confirmed. One wonders whether, after a longer period in culture, the autapses in the coeliac neurons would have become cholinergic, as in the experiments of O'Lague *et al.*[11].

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