

specifically recognizes Lewy bodies<sup>6</sup>. Cortical Lewy bodies immunoreactive to PER2 had a similar morphology to the ubiquitin- and neurofilament-positive Lewy bodies in that they had round, oval or irregular shapes and frequently displaced the nucleus to one side (Fig. 2c).

The strong  $\alpha$ -synuclein staining of brainstem-type and cortical Lewy bodies in idiopathic Parkinson's disease and DLB shows that  $\alpha$ -synuclein is a component of the Lewy body. In some familial cases of Parkinson's disease there is an alanine to threonine mutation at residue 53 of  $\alpha$ -synuclein<sup>11</sup>. A major effect of this mutation may be to promote the aggregation of  $\alpha$ -synuclein into filaments, resulting in the formation of Lewy bodies. The Parkinson's disease cases that we studied were non-familial, so at least two distinct pathogenic mechanisms can lead to  $\alpha$ -synuclein aggregation.  $\alpha$ -Synuclein aggregation and Lewy-body formation may be important in the aetiology and pathogenesis of all cases of Parkinson's disease.

As brainstem-type and cortical Lewy bodies from DLB were strongly immunoreactive for  $\alpha$ -synuclein,  $\alpha$ -synuclein aggregation may also underlie Lewy-body formation in this condition. The intracytoplasmic Lewy body is therefore central to the neurodegenerative process, and both Parkinson's disease and DLB may be  $\alpha$ -synuclein diseases.

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Endogenous proviruses as "mementos"?

In a recent News and Views<sup>1</sup>, J. P. Stoye discussed the potential health risks associated with the spread of endogenous proviruses from pigs and primates through the use of their organs for transplantation into humans. Although the risks to patients and the public from horizontal transmission may be as manageable as he represents, we would like to comment on his reference to the presence of vertically transmitted proviruses in the genomes of all mammals as "mementos".

The spread of such parasites throughout the genome of a species is expected to be accompanied by a large number of additional 'random' insertions. Many (perhaps most) of these insertions will be associated with mutations that are ultimately eliminated by natural selection, so the "mementos" are the surviving insertions, those with minimal effects on the host's fitness. For example, laboratory experiments show that the recent and rapid spread of the *P* element throughout the genomes of all *Drosophila melanogaster* in nature was accompanied by enormous transient net reductions in fertility and viability in the population<sup>2,3</sup>. But in a few thousand *Drosophila* generations, there will be only "mementos" of the *P* element in the genomes of *D. melanogaster* (much as in seen in other species of *Drosophila*).

The apparently innocuous presence of these parasites does not mean that they have not caused a great toll in the past. Further, there is evidence that host genomes may have evolved the ability to repress rapid transposition of families of retroviruses<sup>4</sup> or retrotransposable elements<sup>5</sup>, so that mutation of the relevant genes leads to element mobilization. There is therefore a risk that xenotransplantation could result in such mobilization in a foreign genetic background that lacks appropriate genes to repress transposition. Indeed, Stoye notes that mammalian hosts have evolved "adaptations of host viral-receptor proteins" that contain the spread of the endogenous proviruses. The ubiquitous presence of such effective adaptations implies a strong selective force (differential viability and/or fertility) on the hosts in the past.

In the absence of effective control of reproduction, there is a real risk that a germline infection in a xenotransplantation patient could introduce a new and potentially virulently mutagenic endogenous provirus into the human gene pool. Although the risks associated with insertional mutations are distributed over future generations, they are nevertheless great and worthy of serious consideration in the evaluation of risks and benefits inherent to an

expansion of xenotransplantation.

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*Stoye replies*— On the basis of analogies between *P* elements and retroviruses, Langley and Charlesworth suggest that one potential risk associated with xenotransplantation is a form of insertional mutagenesis resulting from germline integrations by retroviruses derived from endogenous proviruses in the engrafted organs. I agree that these elements are potentially hazardous, but I am not convinced that the threat posed by this form of genomic bombardment is great enough to figure significantly in risk-benefit analysis of xenotransplantation. Rather, the much greater risk is that posed by these elements acting as infectious agents of disease.

Experiments in mice show that exogenous infection by retroviruses<sup>6</sup>, or activation of endogenous proviruses<sup>7</sup>, can result in germline infection. However, even under the most favourable circumstances, the number of acquired proviruses seems to be less than one per generation, of which at most one in ten is likely to be mutagenic<sup>8,9</sup>. Increases in the number of germline proviruses will require further cycles of maternal expression followed by oocyte infection<sup>10</sup>, a process predicted to be significantly less efficient than *P*-element mobilization associated with hybrid dysgenesis in *Drosophila*.

To pose any significant risk to human fitness, a very high frequency of horizontal retroviral transmission (followed by infection of the germ line) would be required. For horizontal transmission on such a scale to occur, levels of viraemia associated with unacceptably high probabilities of virally induced disease would almost certainly have to occur. Several groups are currently addressing the question of whether xenotransplantation procedures pose any threat of infectious disease; provided that this concern is met, the threat to the human gene pool seems exceedingly remote.

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