mucosae even from relatively young subjects and subjects without any sign of dementia. This fact, we concluded, is sufficient to raise doubt about the validity of the method proposed in ref. 1.

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TALAMO REPLIES — Kishikawa *et al.* detect τ-like immunoreactivity in nerve fibres in the sub-mucosal region (lamina propria) of the olfactory area of the nose in a various human autopsy cases, concluding that examination of nasal tissue would not be useful for the diagnosis of Alzheimer's disease. It is relevant to note that in our paper[1] we proposed that neuritic abnormalities within the epithelium, not changes in the deeper lamina propia, might be informative in the study of Alzheimer's.

Within the epithelium, neurofilament and τ-like immunoreactivity are seen in these neurites, although neither is detectable in normal olfactory receptor neurons nor in other components of the sensory epithelium. We did not report finding prominent abnormal staining patterns with either of these antibodies in nerve bundles in the lamina propria, and did not suggest that τ-immunoreactive fibres in the lamina propria were a feature peculiar to Alzheimer's.

Further, it is probable that the τ-positive fibres described by Kishikawa *et al.* are not olfactory receptor neuron axons but are deep axon bundles of trigeminal or autonomic fibres expressing both τ and neurofilament protein as normal constituents. Kishikawa *et al.* did not use antibodies (for example to olfactory marker protein) that would identify olfactory axon fascicles and clearly distinguish them from these other deeply located nerve bundles. In addition, the τ antibody they used recognizes normal as well as abnormal τ, so the observed immunoreactivity may not indicate neurodegenerative changes. This probably explains why Kishikawa *et al.* found staining in most normal individuals.

In agreement with Kishikawa *et al.*, we also did not find structures resembling neurofibrillary tangles, nor have we found evidence for plaques stained for β-amyloid peptide, when using antibody provided by D. Selkoe (ref. 1 and our unpublished results). The neurodegenerative changes of olfactory epithelium thus seem to reflect those seen in degenerating brain and dystrophic neurites, but do not replicate them exactly.

A second issue raised by Kishikawa *et al.* is whether examination of the olfactory mucosa is likely to be useful diagnostically. In this case, the use of other probes must be considered. We find that neurodegenerative and phenotypic changes in human olfactory epithelium are not confined to Alzheimer's patients, although they are prominent in that group. Similar abnormalities are observed in a substantial number of non-demented patients (B.R.T. *et al.*, unpublished results; see ref. 8). A further extensive immunostaining study of the epithelial fibre masses with various τ antibodies[14] suggested that one of the antibodies might preferentially react with particular epitopes in dystrophic olfactory neurites in patients with Alzheimer's. Although the olfactory changes do not appear to be associated exclusively with Alzheimer's, the cause for the transformation of the olfactory neurons is unclear; it remains possible that the events that trigger changes in brains affected by Alzheimer's also produce these neuritic changes in the olfactory epithelium.

A question that is still open is whether nasal biopsy could be useful for studies of this type of pathology. Our early studies hinted that pathological regions of the epithelium might be dispersed irregularly among completely degenerated or relatively normal olfactory regions in autopsy tissue. We have now found[15] that the location of the pathological changes in the superficial epithelium is unpredictable from case to case, suggesting that random sampling by biopsy may not reveal the abnormalities. A possible solution to this difficulty would be to develop a method to identify visually the affected area using fibre-optic endoscopy.

In summary, the human olfactory pathology that we have observed appears to be primary epithelial and to involve olfactory neurons; we agree that staining of nerve bundles in the deeper nasal lamina propria with τ antibodies does not appear to be informative for Alzheimer's disease or for other epithelial neuritic disorders.

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# No thermal instability in the Universe

SIR — We wish to correct the conclusion of C. H. (*Nature* **359**, 40–42; 1992), who proposed that if the Universe was reionized by decaying dark matter, the energy of the reionization could fuel an instability which would lead to structure formation. The mechanism proposed was that given a heat source uniformly distributed in space, in a lower density region each particle would receive more energy, increasing its relative temperature and thus thermal pressure. Decaying dark matter would provide a uniform source of fixed energy photons; if the photons are absorbed locally (if the medium is optically thick) and if they are absorbed only by hydrogen (so that each photon deposits the same amount of energy), it would also provide a uniform source of heating.

But this mechanism does not lead to an instability, because the lower pressure resulting from the lower density cancels the increased pressure from the higher temperature. That is, because the thermal energy added per volume is constant and the thermal pressure is a constant times the thermal energy density, a perturbation in density cannot lead (through this mechanism) to a perturbation in pressure. In the discussion leading to equation 2 of the paper cited above it was incorrectly assumed that Im $(\delta \ln n)$ could be ignored; in fact (in this optically thick limit) it is of the same magnitude as the included terms and of opposite signs.

We have performed a complete linear analysis of reionization with a uniform ionizing source. The analysis includes radiative transfer, general expansion, ionization and photon number disequilibrium, thermal conduction, and Compton cooling. It does not include ionization of helium, collisional ionization, other mechanisms of cooling or spectral evolution. We used a plane-wave, harmonic expansion, valid for times and distances small compared to the size and age of the Universe. That analysis confirms that there is no heating instability, though for an extremely narrow region of parameter space it does allow for a cooling instability which is too weak to be cosmologically significant.

At the suggestion of Dr A. Meiksin, we have also searched for instabilities which can occur if the decay photons are sufficiently energetic to ionize helium (manuscript in preparation). Though this heating mechanism can be unstable, the instability is overwhelmed by the stabilizing influence of Compton cooling.

Although these results are not absolutely conclusive, they suggest that such instabilities are unlikely to be important in the formation of cosmic structure.

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