found analytically. But at $p = 0.41$ the phase transition changes character and simultaneously the computational cost of heuristic searches becomes exponentially great. The authors have defined an order parameter for the statistical phase transition, and above $p = 0.41$ they show that this phase transition jumps discontinuously at the transition. But its variation near the transition suggests that there must be critical fluctuations. (The incorrect statement is made[1] that this is new, but in fact it resembles markedly and unexpectedly the Anderson–Yuval–Kosterlitz–Thouless type of defect-mediated transition[5], used to describe melting in two dimensions.)

In addition to the fascinating implications of this unexpected structure for computational complexity theory, where it marks a long-suspected distinction between problems that are in some sense 'usually' simple to solve rather than 'usually' difficult, this is the first direct correlation of a transition in computational complexity with a critical point of a statistical-mechanics transition. For statistical physicists, this 'new' type of transition (but see my parenthetical comment above) may hold unexpected implications. □

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1. Monasson, R., Zecchina, R., Kirkpatrick, S., Selman, B. & Troyansky, L. *Nature* **400,** 133–137 (1999).
2. Mezard, M., Parisi, G. & Virasoro, M. A. *Spin Glass Theory and Beyond* (World Scientific, Singapore, 1987).
3. Kirkpatrick, S. & Selman, B. *Science* **264,** 1297–1301 (1994).
4. Monasson, R. & Zecchina, R. *Phys. Rev. Lett.* **76,** 3881–3885 (1996).
5. Thouless, D. J. in *Topological Quantum Numbers in Non-Relativistic Physics* 109–115 (World Scientific, Singapore, 1998).

Alzheimer's disease

Antibody clears senile plaques

Peter H. St George-Hyslop and David A. Westaway

People suffering from Alzheimer's disease develop a progressive dementia in adulthood, accompanied by three main structural changes in the brain: diffuse loss of neurons in the hippocampus and neocortex; accumulation of intracellular protein deposits termed neurofibrillary tangles; and accumulation of extracellular protein deposits termed amyloid or senile plaques, surrounded by misshapen nerve terminals (dystrophic neurites). A main constituent of these amyloid plaques is the amyloid-β peptide (Aβ), a 40–42-amino-acid protein that is produced through cleavage of the β-amyloid precursor protein (APP). Although Alzheimer's disease can be treated, we can currently neither prevent nor cure it. On page 173 of this issue, however, Schenk *et al.*[1] show that, in a mouse model of Alzheimer's disease, immunization with Aβ inhibits the formation of amyloid plaques and the associated dystrophic neurites.

These results raise the possibility of vaccination with Aβ against human Alzheimer's disease. But before this can be seriously entertained, several questions must be answered. Schenk and colleagues[1] found that high levels of anti-human Aβ antibody were necessary for the effect to be seen in mice. So, can injection with human Aβ induce enough of the antibody? Will immune tolerance (whereby the immune system does not react against the body's own proteins) frustrate this, as it has often done with attempts to target cancers with antibodies? Conversely, is it safe to immunize people with high levels of a protein that is widely expressed outside the protective confines of the blood–brain barrier? When Schenk *et al.* immunized the mutant mice (known as PDAPP mice, because they overexpress a human APP transgene bearing the pathogenic valine-to-phenylalanine mutation at position 717) with human Aβ peptide, they did not see any autoimmune responses. But then, the human Aβ antigen induced much lower levels of antibodies to the endogenous mouse Aβ or APP.

The most critical question is whether depletion of the amyloid plaques is accompanied by an improvement in the behavioural/neurophysiological impairments, and a reduction in the nerve cell death of Alzheimer's disease? In other words, does immunization with Aβ simply clear a neuropathological by-product or can it cure the disease? This question may be difficult to answer because all of the current animal models (based on overexpression of human APP and/or presenilin-1 transgenes bearing missense mutations associated with Alzheimer's disease) provide only a partial model of the human condition. So, although these animals accumulate increased levels of Aβ in the brain and have many amyloid-plaque deposits, they have only subtle behavioural and electrophysiological deficits. More problematically, these animals do not develop neurofibrillary tangles or show significant neurodegeneration (refs 2–4 and D. A. Westaway *et al.*, unpublished observations).

A second set of questions concerns the mechanism by which immunization with Aβ blocks the formation of amyloid plaques. Antibodies against Aβ might act as an artificial chaperone for extracellular Aβ, possibly by binding to Aβ and preventing it from aggregating or from changing into β-pleated-sheet conformation. Alternatively, these antibodies could accelerate clearance of Aβ from the central nervous system through one of several peripheral mechanisms (targeting Aβ for destruction by the peripheral reticuloendothelial system, for example, or reducing the production of Aβ in the periphery). Finally, Aβ might affect immune modulation of inflammatory mechanisms that are thought to be activated in Alzheimer's disease.

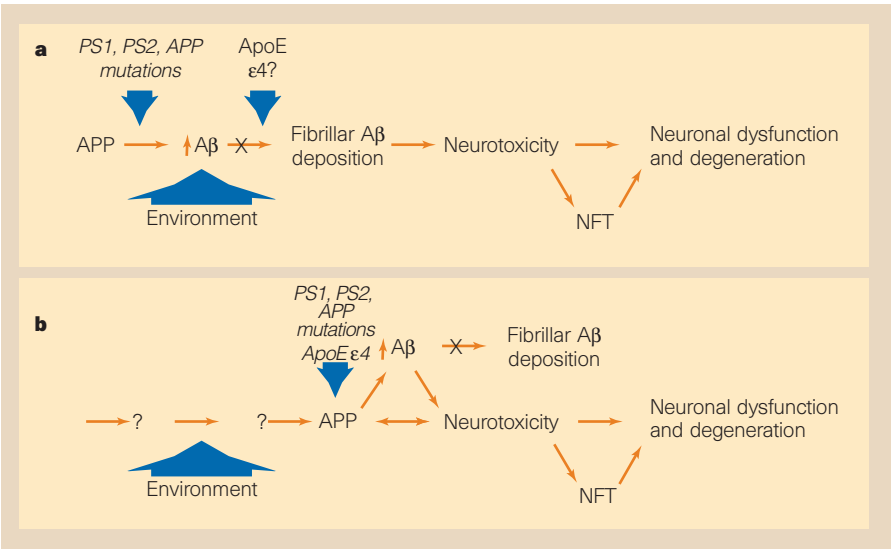

Figure 1 **Controversies about the neuropathological alterations in Alzheimer's disease.** a, **In the 'amyloid cascade' hypothesis, generation of extracellular amyloid-β peptide (Aβ) from the β-amyloid precursor protein (APP) is thought to be central to the pathogenesis of Alzheimer's disease.** b, **An alternative point of view is that the extracellular plaques containing Aβ are an invariant but peripheral event. Large arrows depict putative entry points of environmental and genetic causes of Alzheimer's disease in these pathways. Genetic causes include mutation or polymorphisms in presenilin-1 (PS1), presenilin-2 (PS2), APP and Apolipoprotein E (ApoE). Schenk *et al.*[1] have found that, in a mouse model of Alzheimer's disease, immunization with Aβ presumably blocks (marked with an X) the extracellular deposition of this protein. (NFT, neurofibrillary tangles.)**

Addressing these questions will almost certainly shed new light on an old debate about the pathogenesis of Alzheimer's disease. It is generally accepted that neuronal dysfunction and degeneration underlie the clinical dementia of the disease. But there has long been a controversy as to whether extracellular deposition of fibrillar Aβ in amyloid plaques is part of the biochemical processes that cause the neuronal dysfunction and death, or whether it is merely a by-product of this process.

One school of thought (the 'amyloid cascade' hypothesis) maintains that the processes that cause accumulation of Aβ are central to the pathogenesis of Alzheimer's disease (Fig. 1a). It is unclear whether extracellular accumulation of Aβ (and especially of the longer, potentially more toxic, $Aβ_{42}$ species) is more important than intracellular accumulation. Nevertheless, this hypothesis is supported by several observations. First, in some inherited forms of Alzheimer's disease, missense mutations in APP, presenilin-1 and presenilin-2 (refs 5–7) lead to overproduction of Aβ (ref. 8). Second, $Aβ_{42}$ is toxic both when injected into mammalian brain (especially fibrillar $Aβ_{42}$ in aged primate brain[9]) and when administered to cultured neurons (reviewed in ref. 10). Finally, deposition of Aβ is the earliest neuropathological change detected in people who have mutations in presenilin-1 but do not yet show symptoms of Alzheimer's disease[11].

Opponents of this hypothesis argue that although deposition of extracellular Aβ is an almost invariant event in the pathogenesis of Alzheimer's disease, it need not be the prime cause of the dementia (Fig. 1b). They argue first that the density of the Aβ plaques correlates only poorly with severity of the dementia[12,13]. Second, the degree of dementia is better correlated with the density of cerebral neurofibrillary tangles[13]. Finally they state that, in some of the APP- and presenilin-1-based transgenic mouse models of Alzheimer's disease, the subtle functional deficits occur before the formation of amyloid plaques (ref. 4 and N. Agopyan *et al.*, unpublished observations). Moreover, some cases of Alzheimer's disease lack the typical amyloid plaques[14].

The ability to modulate deposition of extracellular Aβ in the central nervous system while monitoring behavioural and electrophysiological changes may now allow us to determine whether extracellular Aβ deposits are the real villain in Alzheimer's disease. Moreover, if immunization with Aβ is indeed useful against Alzheimer's disease, similar strategies might be applied in the other diseases where extracellular plaques are formed. These might include some forms of prion disease (although, as with Alzheimer's disease, some experiments indicate that extracellular plaques are not neurotoxic[15]), and amyloidotic polyneuropathies (where transthyretin accumulates). This knowledge could even be useful in treating conditions where intracellular deposits are formed, such as Parkinson's disease (α-synuclein) and frontotemporal dementia (tau).□

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1. Schenk, D. *et al. Nature* **400,** 173–177 (1999).
2. Masliah, E. *et al. J. Neurosci.* **16,** 5795–5811 (1996).
3. Chapman, P. F. *et al. Nature Neurosci.* **2,** 271–276 (1999).
4. Moechars, D. *et al. J. Biol. Chem.* **274,** 6483–6492 (1999).
5. Goate, A. M. *et al. Nature* **349,** 704–706 (1991).
6. Sherrington, R. *et al. Nature* **375,** 754–760 (1995).
7. Rogaev, E. I. *et al. Nature* **376,** 775–778 (1995).
8. Scheuner, D. *et al. Nature Med.* **2,** 864–870 (1996).
9. Guela, C. *et al. Nature Med.* **4,** 827–831 (1998).
10. Yankner, B. A. *Neuron* **16,** 921–932 (1996).
11. Lippa, C. F. *et al. Lancet* **352,** 1117–1118 (1998).
12. Berg, L. *et al. Arch. Neurol.* **55,** 326–335 (1998).
13. Terry, R. D., Masliah, E. & Hansen, L. A. in *Alzheimer Disease* (eds Terry, R. D., Katzman, R. & Bick, K. L.) 179–196 (Raven, New York, 1994).
14. Crook, R. *et al. Nature Med.* **4,** 452–455 (1998).
15. Brandner, S. *et al. Nature* **379,** 339–343 (1996).

Condensed-matter physics

Simple metals under pressure

Richard M. Martin

The alkali metals — the monovalent elements in the first column of the periodic table — have long been regarded as prototype 'simple metals' with non-directional metallic bonding. This view is entrenched in the current understanding of solids, which began with the pioneering work of Wigner and Seitz[1]. Under ordinary conditions, all the alkalis from lithium to caesium occur in simple body-centred-cubic (bcc) or close-packed lattices, typical of 'nearly-free electron' metals. The only exception is hydrogen, where protons pair to form H_2 molecules and a condensed molecular solid that is insulating. Because of its place as the first element in the periodic table, it is a Holy Grail of physics to compress hydrogen by pressure until it becomes metallic, like the other alkali metals. It was anticipated that under pressure hydrogen would adopt simpler structures and become closer packed; but such metallic phases have not yet been found by experiments, which have instead revealed transitions to low-symmetry molecular structures[2]. On page 141 of this issue, Neaton and Ashcroft[3] report the unexpected finding that under pressure, lithium (Li) instead acts act like H_2 — that is, the nuclei are predicted to form pairs producing structures similar to condensed phases of H_2.

The predictions of Neaton and Ashcroft are based on state-of-the-art electronic structure calculations, which show that the bcc phase of Li should transform to an orthorhombic structure near 50 gigapascals (Gpa) and to a molecular, semimetallic phase near 100 GPa, finally transforming back to a monatomic metal again at very high pressures. The molecular-like structures favoured by Li at intermediate pressures are related to those thought to occur in molecular hydrogen near its insulator–metal transition. Preliminary calculations[3] also indicate that similar transitions should occur in sodium at much higher pressure and with a much smaller degree of molecular pairing. If this behaviour is actually confirmed by experiments, it will be an achievement for modern theoretical methods, leading to a revised understanding of the alkalis: the apparently simple picture under ordinary conditions being the anomaly, and the range of behaviour under pressure providing new challenges and opportunities.

The 'nearly-free electron' behaviour of the valence electrons of the alkalis is revealed most clearly by their Fermi surfaces, which describe the boundary between occupied and empty electronic states, and which very nearly resemble the sphere that would occur if there were no influence whatsoever from the ion cores. This behaviour is understood in terms of weak electron–ion interactions or 'pseudopotentials' that describe the effective interaction of valence electrons with the ion cores. However, there have been many signs that the alkalis are not so simple. One mystery is the apparent absence of superconductivity, despite the fact that the interactions of the electrons with the lattice vibrations appear to be strong enough to lead to conventional superconductivity, especially in Li (ref. 4). In order to explain such anomalies, large modifications of the Fermi surface have been proposed[5] that would be manifested as unusual optical properties and suppression of superconductivity. It has long been known that deviations of the Fermi surface of Li require a non-local pseudopotential that acts differently for electronic states with zero angular momentum (that is, *s*-states), as opposed to states with higher angular momentum (such as *p*- or *d*-states).

The electronic structure of Li under extreme pressure was calculated by Boettger and Trickey years ago[6]. They found exceptionally large deviations of the Fermi surface from a sphere (also seen by Neaton and Ashcroft; see their Fig. 4 on page 143), which they interpreted as an '*s*–*p*' transition — in which the lowest-energy electronic states change from primarily *s*-like to primarily *p*-like, producing an effective change in the chemistry of Li. Promotion of electrons to unusual valence configurations was observed long ago in another