precursors of the bundle-sheath components of C_4 photosynthesis, this raises some evolutionary questions. When did these cells first occur, and so when might this route to C_4 metabolism have first been available? Decreasing CO_2 levels over the past 20 million years or so, in the Upper Tertiary and Quaternary periods, are known to have been an important factor in the evolution of C_4 metabolism in one of the main groups of higher plants, the flowering plants. But there were also low atmospheric CO_2 levels in the Upper Palaeozoic some 300 million years ago, over 100 million years after the first known higher plants[6]. Oxygen levels in the Upper Palaeozoic atmosphere were higher than today[7]. Combined with low CO_2 levels, this would have decreased the rate of C_3 photosynthesis as a result of the kinetic properties of Rubisco[8], and favoured the evolution of C_4 metabolism. But C_3 metabolism was the main — perhaps the only[9] — mechanism of photosynthesis in the Upper Palaeozoic.

The Upper Palaeozoic forerunners of two of the other major groups of higher plants, the early ferns and conifers, probably did not use the C_4 pathway. Might that have been because the anatomy and physiology of their primary vascular tissue were inappropriate for the photosynthetic mechanism identified by Hibberd and Quick? That is one possibility. But despite the abundant fossil evidence of vascular tissue in Upper Palaeozoic plants, it is not clear whether the associated cells could photosynthesize. So another possibility is that the default condition for the cells of all higher plants, when exposed to the light, was the development of photosynthetic capacity; suppressing that capacity was an evolutionarily derived state. On these grounds, photosynthesis in vascular tissue would have been at least as common in the past as it is now, when chlorophyll-containing cells are associated with vascular tissue in 30 families.

Hibberd and Quick[2] have not said the last word on the evolution of C_4 photosynthesis. But their work makes a significant contribution, not least in pointing to several new lines of investigation. ■

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Huntington's disease

Accomplices to neuronal death

Mark P. Mattson

The shaky movements of people with Huntington's disease are caused by death of a specific group of nerve cells. One culprit — the mutant huntingtin protein — is well known. Another has now been discovered.

When you lift your coffee cup or turn the pages of this journal, you are carrying out a 'voluntary' action. Such movements are produced in response to complicated sequences of nerve cells, and are coordinated by the striatum region of the brain. The job of this region is to inhibit particular neurons in the brain and spinal cord that are not required for a given action. So damage to the striatum can result in uncontrolled body movements — a scenario that occurs in people with Huntington's disease. This inherited, age-related disease is caused by the abnormal lengthening of the repeated sequence CAGCAGCAG… in the gene encoding the huntingtin protein, resulting in long stretches of the amino acid glutamine within the protein. Expression of mutant huntingtin in mice leads to the death of striatal neurons and a neurological disorder that is similar to Huntington's disease[1]. Although the exact details are unclear, the molecular and cellular mechanisms by which mutant huntingtin kills striatal neurons are beginning to be unravelled. Writing in *Nature Cell Biology*, Gervais and colleagues[2] add more pieces to the puzzle.

It was already known that mutant huntingtin somehow triggers apoptosis — a process by which cells effectively commit suicide, systematically chewing up their DNA and degrading their proteins and organelles. In fact, apoptosis is increasingly being implicated in neurodegenerative disorders, from Alzheimer's and Parkinson's diseases to strokes[3]. The abnormality that triggers apoptosis may be different in each disorder; for example, Alzheimer's disease is characterized by the abnormal accumulation of amyloid-β peptide, and neuronal deaths in strokes are triggered by a shortage of oxygen supply to the brain. But in each case apoptosis is carried out by cascades of protein-cleaving enzymes called caspases. In particular, caspase-3 and caspase-8 have

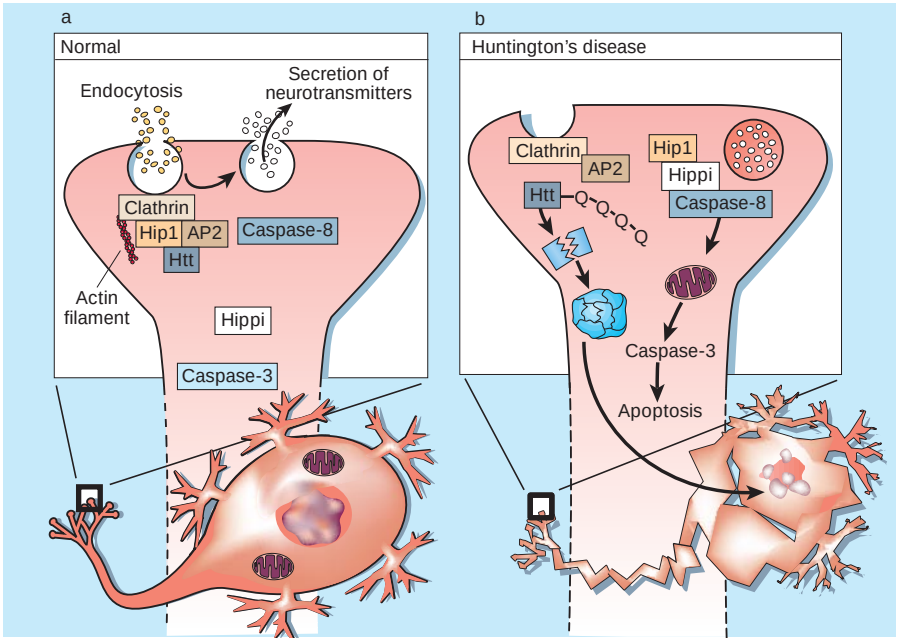

Figure 1 **Possible functions of the normal and mutant huntingtin protein.** a, **In normal nerve cells, huntingtin (Htt) can form a complex with the proteins Hip1, clathrin and AP2. Clathrin and AP2 (and so perhaps Htt) are involved in endocytosis — the internalization of sections of the plasma membrane — which is crucial in allowing neurons to communicate by secreting neurotransmitters.** b, **In patients with Huntington's disease, the Htt protein has an abnormally long tract of glutamine (Q) amino acids. This mutant protein may lead to abnormal endocytosis and secretion in neurons. In addition, it causes striatal neurons to die by the process of apoptosis. Gervais *et al.*[2] show that the long tract of glutamines weakens Htt's interaction with Hip1, which is then free to bind the protein Hippi, and so to activate apoptosis through caspase-8 and caspase-3. Caspase-3 also cleaves Htt, producing fragments that clump together and form inclusions in the neuron and its nucleus.**

100 YEARS AGO

We are glad to learn that the gliding experiments with which Lilienthal and Pilcher sought to investigate the balance and stability of machines supported by aëroplanes and aërocurves have not been discontinued since the death of these two investigators. A great deal of valuable work has already been done in America by Mr. Octave Chanute, and in conjunction with him by Mr. Herring, both of whom have attained results in advance of those previously achieved, by the use of machines provided with movable wings. Still more recently, i.e. from October 1900 onwards, two other workers have attacked the problem, namely, Mr. Wilbur Wright and Mr. Orville Wright, of Dayton, Ohio. Mr. Wilbur Wright adopts a two-surfaced machine and assumes a horizontal position when gliding, with the view of diminishing head resistance. He has successfully worked with a surface area of double that used by previous experimenters, and has on several occasions extricated himself from the dangerous position in which Lilienthal and other observers have found themselves when suddenly brought to rest in a high wind.

From *Nature* 23 January 1902.

50 YEARS AGO

Is there an æther? **In his recent communication Prof. Dirac has said that in his new formulation of electrodynamics a preferred motion exists at each point of space. A preferred motion is also given at each point of space by cosmological observations (apparent isotropy of distant red-shift effects). It is of interest whether any local physical effects are associated with this cosmologically preferred state of motion, and the analogous question can be asked with respect to Dirac's formulation. We have argued that the first question may be answered in terms of the theory of continual creation (the steady-state theory of the universe), where the cosmologically preferred motion is identified with the velocity of newly created particles. Dirac answers the second question by saying that a small charge placed in a vacuum would possess the particular velocity associated with the potentials in his theory. The concept of introducing a charge into a vacuum, without fields destroying the vacuum character of the region, is given physical reality in a theory of continual creation. H. Bondi & T. Gold**

From *Nature* 26 January 1952.

been implicated in neuronal death in such diseases[3].

Caspases are also presumed to be involved in Huntington's disease. They are activated in striatal neurons in Huntington's patients, and in cell-culture and animal models of the disease[3]. Moreover, drugs that inhibit caspases can protect striatal neurons from death in such model systems. But the specific mechanism by which mutant huntingtin triggers the apoptotic caspase cascade has been a mystery, with insufficient evidence available to indict any particular suspect. Previous studies[4] had found that mutant huntingtin leads to the activation of caspase-8. Other investigators[5] have shown that normal huntingtin interacts with a protein known as Hip1. But it was unclear whether and how that interaction is related to Huntington's disease.

Gervais and colleagues[2] now provide an answer. Their studies of cultured cells show that lengthening the tract of glutamine amino acids in huntingtin weakens this protein's interaction with Hip1 to the extent that it is released. Hip1 then interacts with a newly identified protein, Hippi, that appears to be essential for forming a 'death-effector complex' involving caspase-8, thereby setting off the apoptotic cascade. In this cascade, activation of caspase-8 can trigger alterations in mitochondria — the cellular powerhouses — which then release the cytochrome *c* protein; this in turn forms a protein complex called the 'apoptosome', which activates caspase-3. Caspase-8 may also bypass mitochondria and activate the apoptosome directly. Interestingly, caspase-3 cleaves huntingtin, releasing a fragment that can self-aggregate and form inclusions in the cell and nucleus. It is unclear whether these inclusions are required for neuronal death in Huntington's disease, because caspase-3 can kill neurons independently.

Gervais *et al.*'s results[2] show that Hippi is critical for the death-promoting effects of mutant huntingtin in cultured cells. But considerable further work will be required to establish whether this occurs in Huntington's patients. We need to know in what cells and at what levels Hippi is expressed normally in the human brain, and whether its expression or subcellular localization is changed in Huntington's patients in a way that is related to the selective vulnerability of striatal neurons. Another question is whether there is any relationship between huntingtin, Hip1, Hippi and the perturbed cellular energy metabolism that is a major feature of Huntington's disease[6].

Moreover, inherited expansions of tracts of 'trinucleotide repeats' (such as CAG in Huntington's disease) occur in other genes, and in several cases these expansions also cause neurological disorders characterized by the dysfunction and death of neurons that control body movements. Two examples are spinocerebellar ataxia and Kennedy's disease[7]. It remains to be seen whether Hip1 and Hippi have similar roles in triggering apoptosis in these disorders. Finally, alterations in mitochondria are central to the development of Huntington's disease and perhaps to neuronal death. So a further question is whether the Hippi–caspase pathway lies upstream of these mitochondrial changes. If so, how does this pathway interact with other proteins, such as Par4 and members of the Bcl2 protein family[3,8], that control apoptosis at a pre-mitochondrial step?

Beyond their potential implications for preventing and treating Huntington's disease, studies of the pathogenic effects of mutant huntingtin are also revealing the normal function of this protein in neurons (Fig. 1). Several findings are consistent with huntingtin being involved in regulating 'synaptic plasticity' — the ability of neurons to change the strength of their connections (synapses) with other neurons. When neurons communicate, small membrane-clad sacks filled with neurotransmitters in the signal-transmitting (presynaptic) neuron fuse with the neuron's plasma membrane. The neurotransmitters are thereby released and diffuse away, to be picked up by receptor molecules on the extensions (dendrites) of a receiving (postsynaptic) neuron. Several membrane-transport processes are involved, including vesicle fusion with the plasma membrane and the internalization (by 'endocytosis') of excess plasma membrane. The receptors on the receiving neuron can also be internalized by endocytosis and recycled.

Proteins called clathrin and adaptor protein-2 (AP2) are needed for endocytosis, and clathrin-rich endocytotic zones are present in presynaptic nerve terminals, where they may link membrane components with the actin-based cellular 'skeleton'[9]. Hip1 interacts with both AP2 and clathrin[10], and it seems that huntingtin is associated with clathrin-coated membranes along dendrites[11]. The implication is that normal huntingtin has both presynaptic and postsynaptic functions, possibly in processes such as neurotransmitter release and receptor recycling — all of which may contribute to synaptic plasticity.

Gervais *et al.*'s results[2] suggest that mutations in huntingtin might, by reducing its interaction with Hip1, alter endocytotic or secretory processes, leading to synaptic dysfunction and the activation of caspase cascades specifically at synapses. Indeed, apoptotic biochemical cascades involving caspases can be triggered in specific regions of neurons, and may then propagate the cell-death signal to the nucleus[12]. The local activation of caspases may also affect synaptic plasticity and the structural remodelling of synapses[13]. So, as details of the cellular and molecular alterations that sentence neurons to death in trinucleotide-repeat disorders are revealed, so too are the intricate mechanisms that allow neuronal circuits to carry

out their functions and adapt to the environmental demands of ageing, such as impaired energy metabolism. ■

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High-temperature superconductivity

Quantum salad dressing

Jan Zaanen

The mystery of how electrons in a high-temperature superconductor flow without resistance grows deeper. New pictures at the atomic scale reveal two electronic phases that — like oil and vinegar — do not easily mix.

According to quantum mechanics, when space is the same everywhere, a particle should be everywhere at the same time. In low-temperature metals and superconductors, this principle rules the waves of the quantum fluids formed by the electrons. Under such conditions, electronic fluids seem remarkably featureless and insensitive to imperfections in the material. For instance, in a conventional superconductor the structure of the crystal lattice must be severely messed up to get a noticeable response from the superconducting electrons. But the high-temperature superconductivity found in certain copper oxide compounds is different. Quantum physics is still in charge but the underlying quantum fluids do not behave like their low-temperature counterparts. On page 412 of this issue, Lang *et al.*[1] take a direct look at this electronic fluid at the nanometre scale, using scanning tunnelling microscopy (STM)[2]. Instead of the implacable perfection of the conventional superconductor, they find it to be rather messy.

What does the fluid look like? Imagine pouring salad dressing (a mixture of oil and vinegar) on to a plate covered with spots of fat. The result is droplets of vinegar immersed in an oily matrix. If the vinegar were superconductor and the oily matrix were a mystery state of electronic matter called the pseudogap phase, the result would be similar to what Lang *et al.* saw. (The fatty spots represent imperfections in the crystal lattice of the superconductor.) Until now, all we've been able to see at the macroscopic scale is the superconducting droplets merging together, as if the plate's contents as a whole turn into pure vinegar. This merging occurs because of a quantum effect called Josephson coupling. The nanoscale images obtained by Lang *et al.* help us probe beyond the macroscopic surface of this electron system.

Understanding the quantum behaviour of a single electron is hard enough, but there are approximately 10^{23} strongly interacting electrons in every gram of earthly matter. Fortunately the basic rules simplify when the system becomes big. The secret of conventional quantum fluids is that the particles seem to forget that they interact when the system size is scaled up. But they keep their quantum-mechanical habit of spreading out across all the space, and their quantum-statistical nature: fermions (electrons) turn into a Fermi gas (normal metals), and bosons (pairs of electrons) turn into a Bose–Einstein condensate (superconductors).

This is what lies behind the implacable perfection of conventional quantum fluids: the system of particles inherits its basic properties directly from its constituents. But condensed-matter physics is increasingly concerned with quantum systems that do not conform to this description — such as the electron system of the high-temperature superconductors. Despite unprecedented research activity (approximately 100,000 papers since its discovery in 1987), high-temperature superconductivity seems as mysterious as ever. Part of its continuing fascination for physicists is its potential to reveal fundamental insights into the collective behaviour of quantum particles[3,4].

I've already given away the punch-line of Lang and colleagues' result[1]: the electron system of their superconductor looks like salad dressing. But there is deeper meaning to this kitchen-table metaphor — the STM pictures are messy because the superconducting electrons do not forget their interactions when they turn into a quantum fluid. Instead, the electronic matter is still strongly interacting, causing it to act in a highly collective way. Such collective behaviour carries its own logic that supersedes even the differences between classical and quantum physics, allowing me to use everyday phenomena to describe what is happening.

To explain further, salad dressing starts out as protons, neutrons and electrons. If these were non-interacting, salad dressing would remain featureless. Instead, these entities bind into lipid, acetic acid and water molecules, which in turn form two strongly interacting, immiscible fluids: vinegar and oil. Something similar happens in the high-temperature superconductors. In the beginning there are electrons and some crystal-lattice vibrations. These are strongly interacting and the electrons quickly lose their identity and morph into a collective phase with its own emergent properties. Apparently, there are two of these phases — the 'superconducting' and the 'pseudogap' phases — but they do not easily mix. This highly collective electron matter reacts strongly to imperfections in the superconductor (probably missing oxygen atoms in the crystal lattice), causing the droplet picture.

The superconducting phase shares at least some properties with a conventional superconductor, but the pseudogap phase is still a mystery. There are several reasons why it could exist. Initially the pseudogap phase was thought to correspond to a high-temperature precursor of the superconducting state, in which the electrons formed pairs that did not undergo Bose–Einstein condensation until the temperatures dropped low enough[2]. More recently it was thought to be a novel quantum state of matter characterized by an exotic form of order that is difficult to observe experimentally (hidden order)[4]. Theorists came up with several ingenious proposals regarding the nature of this order, such as the flux and *d*-density wave orders[5,6]. Lang *et al.*'s observation of a two-phase mixture at low temperatures makes the high-temperature-precursor explanation less likely, as the pseudogap phase can exist simultaneously with the superconducting state. But it does give strong support to the notion that the pseudogap phase is a separate state of matter.

Lang *et al.* also discovered a very strange property of the pseudogap phase. To investigate the differences between the two phases they introduced nickel impurities into some of their samples. These impurities produce STM fingerprints in the superconducting phase known as 'impurity resonances'. According to theory, the authors should have found a similar, but modified, pattern of impurity resonances in the pseudogap regions. Instead, their measurements show that the resonances disappear completely. This is a serious challenge for existing theories, which are invariably based on the assumption that both phases are very similar on atomic scales, with differences emerging only on larger scales. So if the impurity resonances look drastically different in the pseudogap and superconducting phase, the phases must be dissimilar at the atomic scale. Again the salad-dressing metaphor is helpful — it seems that only a few