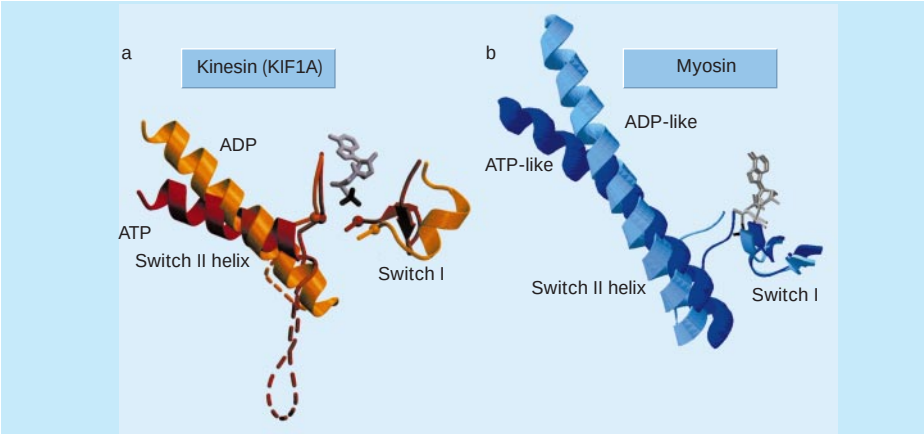

Figure 1 **Comparison of the switch I and switch II regions of two molecular motor proteins.** a, **A kinesin protein (KIF1A; based on Fig. 1c, page 440) and** b, **myosin from *Dictyostelium*.** a, **Orange denotes KIF1A bound to ADP; red denotes KIF1A bound to AMPPCP (a non-hydrolysable analogue of ATP), as determined by Kikkawa *et al.*[1]. The dashed line represents one of the loops in the switch II cluster.** b, **The region near the nucleotide-binding site in myosin. Light blue denotes the ADP-like state (myosin bound to MgADP-BeFx (ref. 7); structure extracted from the RCSB Protein Data Base, accession number 1MMD). The long, straight switch II helix here is bent and slightly shifted in the ATP-like state (myosin bound to MgADP-vanadate[8], dark blue; accession number 1VOM). The two structures of each motor are aligned on the nucleotide-binding loop (omitted for clarity), so that the nucleotide (grey) can serve as a reference for the structural changes in switch I and switch II. The small rotation of the switch II helix in myosin resembles that of the analogous structure in KIF1A, even though the translation of this conformational change into movement differs for these two motors[9].**

fitted ('docked') into these contours to determine whether the structures obtained by crystallization correspond to actual conformations of kinesin heads on microtubules. These docking studies add an interesting twist: they suggest that the switch II cluster stays fixed in one position, while the bulk of the motor domain rotates by about 20° relative to the microtubule. The authors propose that this 'screw-cap' rotation tightens the grip of the motor domain on the microtubule surface when ATP occupies the nucleotide-binding site, presumably because the α4 helix slides a tiny bit deeper into a complementary groove in the microtubule surface.

Not everybody in the kinesin field is likely to agree with these docking studies — they involve a certain degree of eye-balling and rarely produce a perfect match. But the authors offer a testable working model. In their view, the 20° twist also produces enough displacement of the motor tip towards one end of the microtubule to bias movement in that direction. It remains to be seen whether this displacement (just a few ångströms) does indeed generate sufficient directional bias. Kikkawa *et al.* also suggest that their findings, obtained using a monomeric, and therefore somewhat unusual, kinesin, can be extended to other proteins in the kinesin family. A comparison of the monomeric kinesin with crystal structures of other kinesins suggests that this is plausible, but confirmation is needed.

Kikkawa *et al.*'s proposal of a twist-on ATP-bound state and a twist-off ADP-bound state for kinesin, allowing the motor to alternate between tight and weak binding conformations, is likely to stimulate much discussion. It certainly is easy to remember. Next time you untwist the cap on a bottle of your favourite drink, think of kinesin. ■

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Bose–Einstein condensation

Getting excited about helium

Randall G. Hulet

Creating a quantum fluid from a gas of excited helium atoms is not easy — the atoms tend to self-destruct. But two groups in France have pulled it off.

When liquid helium is cooled to a temperature of about two degrees above absolute zero (2 kelvin), something strange and spectacular happens: it suddenly acquires the ability to flow without friction. This transformation, first observed in the 1930s and known as Bose–Einstein condensation (BEC), occurs when the helium atoms join together into a single quantum state (some of the history is recounted in the obituary of Jack Allen on page 436). The collective behaviour of BEC is responsible not only for the 'super' in these liquid-helium superfluids, but also, in an indirect sense, for superconductivity in solids. Now helium is once again making BEC news, thanks to breakthroughs by two groups in France. Writing in *Science* and *Physical Review Letters*, Robert *et al.*[1] and Pereira Dos Santos *et al.*[2] report the creation of Bose–Einstein condensates of helium, but this time in a gas of excited atoms.

Although helium now joins rubidium[3], lithium[4], sodium[5] and hydrogen[6] as elements that have been turned into condensates in the gas phase, the new work is not just another step through the periodic table. The results are exciting because, for the first time, the helium atoms are not in the lowest electronic state, the ground state, when BEC occurs. Instead, they are 'metastable' atoms that have nearly 20 electron volts (eV) of internal energy. This excitation energy is huge compared with the thermal energy of a supercooled condensate (just 10^{-10} eV per atom).

Such a large internal energy offers a route to detecting single atoms, but it also posed a serious challenge to achieving BEC in the first place. As shown in Fig. 1a (overleaf), the collision of two metastable helium atoms (He*) can result in the ionization of one of the He* atoms, leaving the other in the ground state. Because the metastable state has such a large excitation energy, the rate of ion production (Penning ionization) is extraordinarily large — so large, in fact, that the gas of metastable atoms destroys itself in just a few milliseconds.

The success of the new experiments hinges on a bold prediction by Shlyapnikov, Walraven and collaborators[7] that the rate of Penning ionization could be reduced by several orders of magnitude, perhaps by as much as a factor of 10,000, if the He* atoms were spin polarized. Particles like atoms and electrons have a quantum-mechanical spin and can be thought of as tiny bar

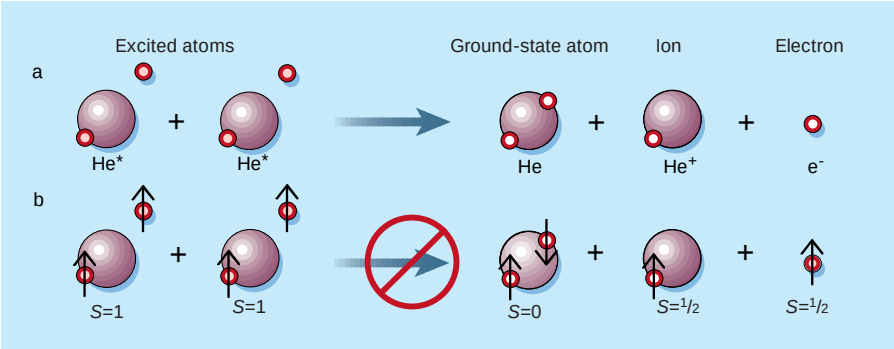

Figure 1 **Collisions between excited helium atoms.** a, **The collision of two unpolarized metastable helium atoms (He*) results in Penning ionization, producing a ground-state helium atom, a helium ion (He^+) and a free electron. The rate for this process is so large that it would prevent Bose–Einstein condensation.** b, **Penning ionization can be suppressed by spin polarizing the atomic electrons. Because spin must be conserved, two polarized He* atoms are unable to undergo Penning ionization. The initial atoms have total spin, $S = 2$ (each of the four electrons contributes 1/2), whereas the products can have spin no greater than 1. Two groups[1,2] have now used this process to achieve Bose–Einstein condensation in a metastable helium gas.**

magnets. Each electron has a spin, *S*, of 1/2 and can point either up or down. When helium atoms are spin polarized, the total spin of two He* atoms is the sum of the spins of their four electrons ($S = 2$). After Penning ionization, the total spin of the products — a ground-state helium atom with zero spin, a He^+ ion and a free electron each with spin 1/2 — can be no more than 1 (Fig. 1b). Because spin must be conserved in quantum mechanics, Penning ionization is severely suppressed. Spurred on by this prediction, several groups began experiments to make BEC in spin-polarized He*.

For BEC to occur, the quantum wavelengths of the atoms must be greater than their average separation, which for liquid helium is about 0.4 nanometres. For experiments on liquid helium, this condition is met only at temperatures below 2.2 K. But for helium gas, in which the density is roughly a billion times lower, ultralow temperatures of around 1 μK are needed. Both groups in France achieve this by using what are now routine methods of laser cooling, magnetic trapping and forced evaporative cooling. Magnetic traps confine magnetic atoms, such as He*, in bowl-shaped magnetic fields. A bonus of this technique is that the magnetically trapped atoms are necessarily spin polarized, and hence meet the condition required for suppressing Penning ionization. A new challenge for these BEC experiments is producing metastable helium. Because no lasers operate at the extreme ultraviolet wavelength of 63 nanometres required to resonantly excite ground-state helium, the researchers had to rely on an electrical discharge to provide the necessary excitation energy. This process is woefully inefficient, converting only one in every 100,000 atoms.

Although similar in every other respect, the two new experiments differ significantly in their methods for detecting BEC. A signature of BEC is the sudden appearance of atoms moving very slowly. Whereas Pereira Dos Santos *et al.*[2] used optical absorption to image the He*, a common technique in alkali-metal BEC experiments, Robert *et al.*[1] exploited the 20 eV of excitation energy released when He* hits a surface. When the He* atom falls on a charged-particle detector it is readily ionized and initiates a shower of electrons that are easily amplified and detected as an electrical pulse. This high detection efficiency is one of the things that makes a condensate of He* atoms different from the alkali condensates or liquid helium.

At a sufficiently low temperature of about 5 μK, and with 10^5 to 10^6 atoms in their traps, both teams observed the characteristic low-velocity signal of BEC, confirming that Penning ionization is suppressed in a gas of spin-polarized He*. Pereira Dos Santos *et al.*[2] report the suppression to be a factor of at least 2,000, in agreement with theory. Both groups also find that the elastic scattering cross-section, an important quantity governing the rate at which atoms collide and come into thermal equilibrium, is especially large for He*. It was the fortunate combination of a high rate for achieving thermal equilibrium and a low rate of Penning ionization that made these experiments successful.

What's next for helium condensates? The ability to detect He* atoms with almost perfect efficiency clears the way for some intriguing applications. One promising direction to explore is what happens to BEC, which by definition is a many-body phenomenon, when there are just a few atoms. Many questions regarding the fluctuations of condensate number and quantum phase may be addressed. A second avenue is to use He* for atom lithography, in which nanoscale features are drawn on a surface by directly depositing atoms. Previous experimenters have exposed a surface to beams of He* to deposit features as fine as a few tens

100 YEARS AGO

Mr. Andrew Carnegie, the American millionaire, has come forward with a proposal to provide free University education to the youth, both male and female, of Scotland, and offers to place the sum of two millions of pounds in the hands of trustees… There can be but one opinion regarding the large-heartedness which prompts so magnificent a benefaction, and the whole nation will hope that a sound result may be obtained through so noble a gift… Two obvious criticisms evoked by the bare statement that has been made public may, without detracting from the generous intention of the donor, be noted. In the first place, the consequence of the gift as adumbrated must be that secondary education will, in Scotland, alone be unendowed… Secondly, the gift is no endowment of the Scottish Universities, but it may, on the contrary, be an embarrassment to them. It means the creation of some sixteen hundred bursaries, each of the value of nine pounds, in each of the Universities. This will not bring an influx of sixteen hundred students to each University, but, if Mr. Carnegie's intention be realised, we take it there be a considerable increase in the number—sufficient, indeed, to swamp the existing equipment for teaching.
From *Nature* 23 May 1901.

50 YEARS AGO

In the course of experiments on the persistence of deposits from aqueous suspensions of different particle sizes of volatile insecticides, it has been found that the residual toxicity of particles of any one size is influenced considerably by the type of material to which they are applied. Most striking results have been obtained on mud blocks made from 'murram', a lateritic ironstone, used in the construction of walls of houses in Uganda. Crystals of all insecticides used rapidly disappear from the surface of these blocks when they are kept at 78 °F (25 °C), and even those of DDT, which is usually regarded as a contact insecticide with a long residual life, are no longer visible after only a few days… When DDT and 'Dieldrin' crystals are no longer visible on the surface, the mud blocks lose their toxicity to mosquitoes (*Aedes aegypti*, L.) exposed to them for long contact periods.
From *Nature* 26 May 1951.

of nanometres[8,9]. With metastable atoms it may be possible to create more complex patterns using atom holography[10]. The efficiency of these processes, although currently low, could be enhanced significantly with an efficient 'atom laser' constructed from a metastable BEC.

So although Bose–Einstein condensates of He* and liquid helium are composed of the same atomic element, they have very different characteristics. The unique properties of a BEC of metastable helium gas will give researchers a powerful tool with which to learn more about this fascinating state of matter. ■

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RNA interference

The short answer

Brenda L. Bass

One way of seeing what a gene does is to block its messenger RNA and note the effects. New work should make the approach more broadly applicable.

RNA interference (RNAi) was discovered only a few years ago[1], but many scientists find it hard to imagine life without it. Once the sequence of a gene is known, RNAi offers a quick and easy way to determine its function, and the technique is accessible to a scientist in a small lab, as well as to a consortium attempting to assign function to the genes of an entire chromosome[2,3]. But although RNAi is now routine in laboratories studying a wide range of organisms, its use in mammalian cells has been problematic. On page 494 of this issue[4] Tuschl and colleagues describe research that paves the way for successful RNAi in mammalian cells.

The basic idea behind RNAi is shown in the right-hand part of Fig. 1 — this is the sequence-specific pathway indicated by blue arrows. A double-stranded RNA (dsRNA) matching a gene sequence is synthesized *in vitro* and introduced into a cell. The dsRNA feeds into a natural, but poorly understood, biological pathway, and is broken into short pieces called short interfering (si) RNAs[5]. With the help of cellular enzymes that have not yet been well characterized[6], the siRNA triggers the degradation of the messenger RNA that matches its sequence. This often leads to adverse consequences for the organism, evident in an aberrant phenotype, that allow the gene's function to be identified.

RNAi was first discovered in the nematode worm *Caenorhabditis elegans*[1], but is present in many other organisms (the fruitfly *Drosophila*, certain parasitic protozoa, and plants, for instance), and so seems to represent an ancient pathway[7]. Nonetheless, researchers have always been pessimistic about applying RNAi to mammalian cells, because exposing such cells to dsRNA, of any sequence, triggers a global shut-down of protein synthesis[8]. This nonspecific pathway is indicated on the left of Fig. 1 by a red arrow. The lore has been that this pathway would mask any sequence-specific effects that might occur from the RNAi pathway.

But it almost always pays to consider how one's own research fits in with previous observations. Tuschl and colleagues were, it seems, being especially diligent in this respect. Their earlier work showed that the siRNA intermediates themselves could initiate RNAi, at least in non-mammalian cells[5]. However, the nonspecific pathway requires longer dsRNA, and will not occur with dsRNAs shorter than around 30 base pairs[8–10]. They don't say as much in the paper, but one presumes that Tuschl's group began with the idea that, because of this size discrimination, siRNAs might be able to bypass the more global, nonspecific response. They turned out to be right.

First, Tuschl and colleagues[4] tested whether siRNAs could trigger RNAi in mammalian cells, as had been observed in non-mammalian cells. They assayed the ability of siRNA to target various luciferase transgenes, for which gene expression is easily quantified by measuring luminescence. siRNAs were transfected with cationic liposomes into various mammalian tissue culture cells (NIH/3T3, COS-7, HeLa and 293 cells), as well as into a *Drosophila* cell-culture line for comparison. Indeed, the authors observed reproducible, sequence-specific siRNA inhibition in the mammalian cells, with no sign of the nonspecific effects. In contrast, with longer RNAs, luciferase expression was reduced with every dsRNA tested, no matter what its sequence. Superimposed on the nonspecific inhibition was a sequence-specific inhibition, suggesting that both pathways can operate simultaneously. (As shown in Fig. 1, the two pathways probably compete for the long dsRNA.) Importantly, Tuschl and co-workers went on to show that siRNAs are not only effective at targeting the transgene luciferase, but also at targeting naturally occurring, endogenous genes.

Of course, the story is not as neat and tidy as I have described it here. As the authors are

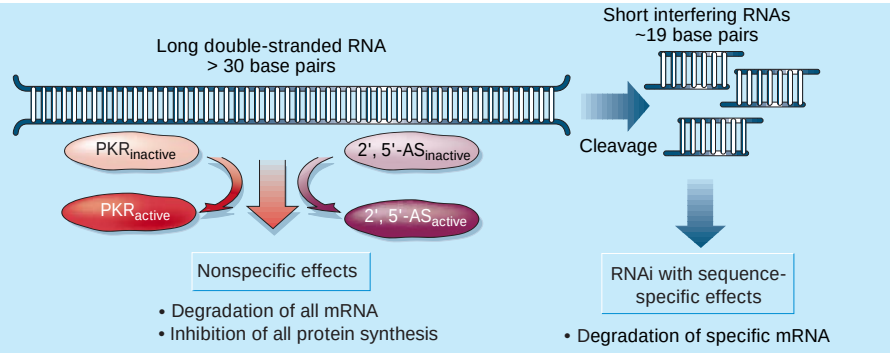

Figure 1 **Mammalian cells have at least two pathways that compete for double-stranded RNA (dsRNA). In the RNAi, or sequence-specific, pathway (blue arrows), the initiating dsRNA is first broken into short interfering (si) RNAs. siRNAs have sense and antisense strands of about 21 nucleotides that form 19 base pairs to leave overhangs of two nucleotides at each 3′ end. siRNAs are thought to provide the sequence information that allows a specific messenger RNA to be targeted for degradation. The nonspecific pathway (red arrow) is triggered by dsRNA of any sequence, as long as it is at least 30 base pairs long. The nonspecific effects occur because dsRNA activates two enzymes: PKR, which in its active form phosphorylates the translation initiation factor eIF2a to shut down all protein synthesis, and 2′, 5′ oligoadenylate synthetase (2′, 5′-AS), which synthesizes a molecule that activates RNase L, a nonspecific enzyme that targets all mRNAs. The nonspecific pathway represents a host response to stress or viral infection; in the second case, the activating dsRNA is thought to derive from viral replication.**