that the mitotic checkpoint is intact in Apc^{min}/Apc^{min} ES cells, supporting the view that APC's function at the kinetochore is structural. Thus, at least in ES cells, APC is required for chromosome segregation.

One important complicating issue is that Apc^{min} cells cannot degrade β-catenin. This raises the possibility that the mitotic defect could be a secondary consequence of altered transcription. Fodde *et al.* address this point by characterizing a targeted *Apc* mutation (Apc^{1638T}) that encodes an APC protein with a less extensive carboxyl-terminal truncation than Apc^{min} and that still contains critical sites for binding components of the β-catenin destruction complex (*11*). It is already known that Apc^{1638T} cells degrade β-catenin as efficiently as their wild-type counterparts. Consistent with an absolute requirement for β-catenin stabilization in the development of colon cancer, Apc^{1638T} homozygous mice are viable and do not get colon cancer (*11*). Now, however, Fodde *et al.* show that Apc^{1638T} ES cells, like Apc^{min} cells, have defects in chromosome segregation and mitosis. Results with the Apc^{1638T} mutant cells provide a strong argument that the functions of APC in β-catenin degradation and mitosis are independent.

There are interesting parallels between APC's proposed involvement in the attachment of microtubules to kinetochores and recent work on the attachment of microtubules to the region below the plasma membrane of yeast cells known as the cortex (see the figure). In yeast, the attachment of microtubules to the cortex is necessary for the correct alignment of the mitotic spindle with the axis of cell division. A key mediator in this process is a protein complex composed of the yeast EB1 ortholog, Bim1p, and a cortical protein, Kar9p (see the figure). Once attached to the ends of microtubules, the Bim1p/EB1-Kar9p complex can link microtubule ends to actin-rich structures at the yeast cell periphery and to actin cables in the daughter cell (*12–15*).

Fodde *et al.* provide evidence that EB1 is also required for the APC-mediated attachment of microtubules to kinetochores. They created cell lines that expressed the EB1-binding domain of APC and, strikingly, these cells had a CIN phenotype. These results suggest unifying themes for how spindle microtubules form attachments. Protein complexes that bind to the ends of microtubules, such as Bim1p/EB1-Kar9 or EB1-APC, may mark the plus ends, distinguishing them from the rest of the microtubule. These complexes may regulate microtubule growth and also may serve as adaptors that link microtubule ends to target sites on kinetochores or at the plasma membrane.

How successfully do the ES cell experiments model the CIN phenotype of colon cancers? One issue is that development of colon cancer involves multiple genetic changes. Although the precise timing of chromosomal instability during the transformation of normal cells into tumor cells is not known, it may occur earlier than previously suspected (if there is a lag before changes in chromosome number become apparent). Fodde *et al.* report that blocking apoptosis in either Apc^{min} or Apc^{1638T} ES cells results in a greater number of aberrant chromosomes than observed in control cells that are able to undergo apoptosis. This is notable because it suggests that the chromosome segregation defect in *Apc* mutant cells could lie silent until an additional genetic "hit" suppresses the mitotic checkpoint or the apoptosis of defective cells. This neatly integrates the new work with the "multiple genetic hit" hypothesis of colon cancer development.

A second key issue is that CIN is a complex phenomenon—it not only involves missegregation of whole chromosomes, but also includes complex rearrangements between chromosomes. When apoptosis is suppressed in either Apc^{min} or Apc^{1638T} ES cells, they develop complex chromosomal rearrangements. It is well-established that defects in the enzyme telomerase (which maintains the ends of chromosomes) can generate chromosomal rearrangements in colon and other epithelial cancers (*16*). However, aberrant mitosis can also lead to broken chromosomes, potentially providing an alternate route for the development of CIN. Indeed, Kaplan *et al.* detected torn chromosomes in metaphase Apc^{min} ES cells. Thus, the *Apc* mutant ES cells recapitulate many characteristics of the CIN phenotype. Ultimately, the key test will come from animal models in which it should be possible to determine whether Apc^{1638T} and other more specific alleles promote CIN and accelerate tumor formation in vivo.

These studies open up new avenues for understanding chromosomal instability and cancer. The desired destination is a realization of how kinetochore attachment, chromosome movement, and cell cycle checkpoints are integrated to prevent CIN. The newly discovered protein complexes at the ends of microtubules may point us in the right direction.

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PERSPECTIVES: QUANTUM PHYSICS

Standing Room Only at the Quantum Scale

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A central tenet of quantum mechanics is that all matter exhibits both wave- and particle-like features. All particles are endowed with a de Broglie wavelength, which is inversely proportional to the particle's momentum and determines its effective "size." When a gas containing many identical particles is confined and cooled, the average momentum can be lowered so far that the typical de Broglie wavelength is larger than the average separation between the particles. In this case, the gas is said to be "degenerate," meaning that the wave functions of neighboring particles overlap. Degenerate gases exhibit two dramatically different types of behavior, depending on whether the identical particles are bosons (such as photons) or fermions (such as electrons). Even in the absence of interactions between the particles, bosons tend to clump together, whereas fermions must avoid one another. The latter thus occupy much more volume in the container.

On page 2570 of this issue, Truscott *et al.* report a direct observation of this remarkable feature of quantum mechanics (*1*). They simultaneously confine a mixture of lithium-6 atoms (which are fermions) and lithium-7 atoms (which are

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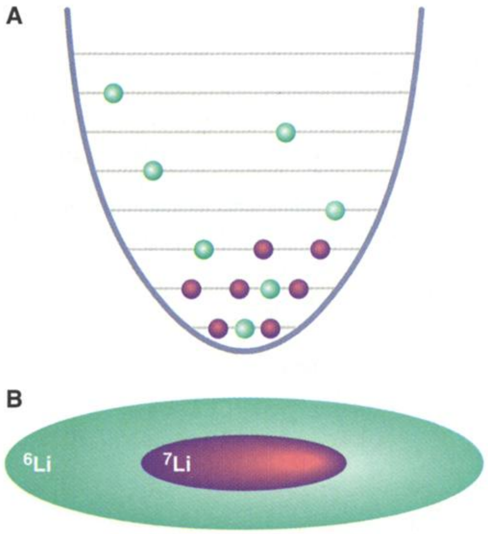
bosons) and cool both gases to about 200 nK. At this temperature, the de Broglie wavelength is several micrometers, comparable to the interparticle spacing. The two gases are at the same temperature in the same container, but the fermionic ^{6}Li gas occupies a much larger volume than the bosonic ^{7}Li gas (see the figure).

Whether a particle is a fermion or boson depends on its intrinsic angular momentum or spin. This will in turn determine their behavior according to the spin-statistics theorem. All particles with half-integer spin are fermions. Familiar examples are the electron, neutron, and proton, all of which have a spin of 1/2. Fermions obey the Pauli exclusion principle, which states that only one identical fermion can occupy a single quantum state of a system. This is why electrons in atoms must fill consecutive energy orbitals, giving rise to the different chemical properties of elements in the periodic table. In contrast, bosons are particles with integer spin and can occupy the same quantum state. The photon (with spin 1) and the graviton (with spin 2) are examples of bosons. Composite particles built out of an even number of fermions behave as bosons, whereas particles containing an odd number of fermions behave as fermions. ^{6}Li contains three protons, three neutrons, and three electrons and is thus a composite fermion. Adding one more neutron to make ^{7}Li creates a composite boson with virtually identical chemical properties but dramatically different behavior in a low-temperature degenerate gas, as demonstrated by Truscott *et al.* (*1*). By comparing the size of degenerate ^{6}Li and ^{7}Li clouds in the same container (a magnetic trap), the authors provide a striking demonstration of the consequences of spin statistics in an elementary system, an ultracold gas of noninteracting identical particles.

The production of a degenerate fermionic gas is also of interest in its own right because it has been achieved in only one other case, potassium-40 (*2*). Degenerate Bose gases (better known as Bose-Einstein condensates) of sodium, rubidium, and lithium have been studied since 1995 (*3–5*), but the production of degenerate Fermi gases posed new challenges. Degenerate Bose gases are produced by using evaporation to cool the gas in a magnetic trap. The hottest atoms are selectively expelled from the trap, leaving colder atoms that rethermalize to a lower temperature through elastic collisions. Unfortunately, this method does not work for fermions. At low temperatures, the Pauli exclusion principle forces these particles to be farther apart than the range of the collisional interaction, and they therefore cannot collide and rethermalize.

To overcome this problem, there must be two different species in the trap. In Truscott *et al.*'s experiment, a large sample of bosonic ^{7}Li is used as a refrigerator to cool a small sample of fermionic ^{6}Li. ^{7}Li and ^{6}Li are allowed to collide because they are not identical, and the two species can thus come to equilibrium at the same temperature, producing a degenerate sample.



Catching two gases with one trap. In Truscott *et al.*'s experiments, ^{7}Li atoms (filled red circles) and ^{6}Li atoms (filled green circles) are simultaneously confined in a magnetic trap (**A**). Near temperatures of absolute zero, the bosonic ^{7}Li atoms occupy the lowest energy levels. In contrast, only one fermionic ^{6}Li atom can occupy a given quantum state. Fermions must therefore avoid one another, creating an effective "Fermi pressure" that causes the Fermi gas to occupy a much larger volume in the magnetic trap compared with the Bose gas as shown in (**B**).

This method, called "sympathetic cooling," was also used by Schreck *et al.* (*6*) to cool ^{6}Li atoms toward degeneracy. DeMarco and Jin (*2*) used a closely related method to cool fermionic ^{40}K to degeneracy. They took advantage of the fact that spins can point in two different directions, enabling two different spin states of the fermionic atom to be trapped simultaneously. This enables collisions and evaporative cooling without the use of bosons. In principle, this approach can also be applied to ^{6}Li, but pairs of spin states that can be magnetically trapped are not stable in this system. This problem has been overcome by using an all-optical trap (*7*) to confine stable pairs of ^{6}Li spin states, enabling evaporative cooling (*8*).

Degenerate Fermi systems are ubiquitous in nature—for example, in neutron stars, nuclear matter, and the electron gas in both normal and superconducting metal—but these systems are often complicated and do not always lend themselves to comparison with theoretical predictions. Now that sources of dilute, degenerate Fermi gases have become available, precise studies can be undertaken, which will further deepen our understanding of these fundamental systems.

Such experiments may, for example, shed light on the physics underlying high-temperature (high-T_c) superconducting materials. Despite their substantial technological importance, these materials are still not well understood. It has been predicted that a two–spin-state mixture of ^{6}Li atoms should undergo a superconducting transition to a superfluid phase as the gas is cooled below a critical temperature (*9*) owing to a large, attractive interaction between ^{6}Li atoms in different spin states (*8*, *10*). In the superfluid phase, pairs of ^{6}Li atoms in different spin states bind together to form Cooper pairs, providing stability and enabling superconducting properties. Observation of this phase transition would permit the systematic study of a superfluid gas in which the temperature, density, and interaction strength can be independently controlled.

For this transition to be observed, however, several new challenges must be addressed. Formation of Cooper pairs has been predicted for certain spin states in both ^{6}Li (*9*) and ^{40}K (*11*), but much lower temperatures must be achieved before the pairing can be observed. Further, the required spin states must be confined at high density in an optical trap in a region free of large magnetic field gradients, which would destroy the pairing. These and other developments are likely to lead to new insights into interacting Fermi gases (*12*).

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