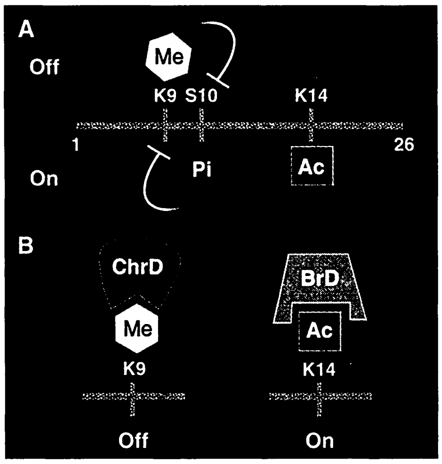

Modifying histones. Modifications to amino acid residues in histone protein H3 and the specialized domains of other proteins that bind to modified residues. **(A)** Dual modification of histone H3 occurs during gene silencing or gene activation. During gene silencing ("Off" state), Lys-9 (K9) is methylated (Me) and Lys-14 (K14) is deacetylated (X). During gene activation ("On" state), Ser-10 (S10) is phosphorylated and Lys-14 is acetylated. Methylation of Lys-9 blocks phosphorylation of Ser-10 and phosphorylation of Ser-10 blocks methylation of Lys-9. **(B)** As a result of these modifications, the chromodomain (ChrD) of regulatory proteins binds to methylated Lys-9 during gene silencing, and the bromodomain (BrD) of regulatory proteins binds to acetylated Lys-14 during gene activation.

ic DNA sequences associated with H3–Lys-9 methylation. The authors found that histone methylation at centromeres requires Clr4 methyltransferase activity and also depends on a histone deacetylase that specifically removes the acetyl moiety from the nearby Lys-14 of histone H3. Because Lys-14 is a common target of acetyltransferases associated with gene activation, these results suggest that deacetylation of Lys-14 leads to methylation of Lys-9 in an obligatory sequence. A second class of proteins, typified by HP1 (heterochromatin protein 1) in the fly, is also required for the maintenance of gene silencing. In fission yeast, the HP1 homolog Swi6 is localized to the heterochromatin of centromeres. The Nakayama *et al.* work (*1*), and a second study by Bannister *et al.* (*6*), demonstrate that localization of Swi6 to heterochromatin also requires Clr4 methyltransferase activity. Thus, it appears that deacetylation of H3 leads to its methylation, which then results in the localization of Swi6 to heterochromatin. Previous data have indicated that Swi6 expands across the heterochromatic region, presumably creating a unique silencing chromatin structure. Taken together, this work suggests an obligatory sequence of histone modifications that recruits structural proteins to DNA, resulting in the creation of heterochromatin.

The sequence of histone modifications during gene silencing—first, deacetylation of Lys-14, and then methylation of Lys-9—has a precedent in the dual ordered modifications of histone H3 during gene activation. Histone phosphorylation at serine-10 precedes and promotes acetylation at Lys-14 (*9*, *10*). Thus, together these studies of gene silencing and activation suggest that histone H3 exists in two modification states: an "Off" state characterized by methylation of Lys-9 and deacetylation of Lys-14, and an "On" state wherein Ser-10 is phosphorylated and Lys-14 is acetylated (see the figure). Interestingly, in vitro methylation of Lys-9 inhibits phosphorylation of Ser-10 and phosphorylation of Ser-10 inhibits methylation of Lys-9 (*8*). This dual arrangement could serve to reinforce gene silencing or activation in vivo.

The next compelling question is exactly how these histone modifications alter transcription. A recently advanced idea, the "histone code" hypothesis (*11*, *12*), holds that covalent modifications of histones constitute an intricate pattern that creates a docking surface with which the modules of other proteins can interact. Proteins containing these modules bind to chromatin to alter its structure, provide additional enzymatic activity, or to target other regulatory proteins. Initial support for the docking idea comes from histone acetylation: The bromodomain present in histone acetyltransferases and in other proteins that interact with chromatin binds with higher affinity to peptides bearing acetylated lysine than to unmodified peptides (*13*, *14*). Two recent papers (*6*, *7*) that also examine how histone methylation regulates the silencing of heterochromatin provide strong support for the docking proposal. These studies analyze a domain, called the chromodomain, found in heterochromatin-associated proteins, such as HP1 and Swi6. The chromodomain binds with high affinity to histone H3 peptides bearing methylated Lys-9 both in vitro and in vivo. Thus, a reciprocal docking mechanism may consist of, on the one hand, binding of a bromodomain to acetylated histone during gene activation, and on the other, binding of a chromodomain to methylated histone during gene silencing (see the figure). All chromodomain proteins, however, do not bind to methylated Lys-9 of histone H3 (*6*), prompting speculation that there may be additional patterns of histone modifications (and even other targeting mechanisms) (*15*) that specify the binding of other chromodomain proteins. A looming challenge will be to determine the histone modification "code" that specifies the binding to chromatin of numerous other domains in chromatin-associated proteins.

Thus, the silencing and activation of genes may require multiple modifications of histones, which generate unique surfaces for the binding of proteins that carry out further chromatin-related processes. The modification patterns that exist in these histones are just beginning to be decoded, yet it is already abundantly clear that the many distinct covalent modifications of chromatin, although initially confusing, are an important aspect of genomic regulation.

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PERSPECTIVES: SUPERCONDUCTIVITY

How Could We Miss It?

A. M. Campbell

In January of this year, the world of superconductivity was stunned by the announcement that the compound MgB_2 was superconducting at a critical temperature T_c of 39 K. Perhaps "astonished" is more accurate than "stunned," because every superconductivity laboratory in the world immediately began to make measurements on this new material and dash into print. Fifty preprints had been posted on the Web by the end of February—before the original paper was even published (*1*). On page 75 of this issue, Monteverde *et al.* (*2*) investigate the superconducting mechanism of MgB_2. The results show similarities with high-T_c oxide superconductors, although other measurements suggest that the material has more in common with low-T_c superconductors. This is an important question because it has proved extremely difficult to make useful wires out of high-T_c superconductors.

Superconductivity—in which the resistance of a material to electrical conduction becomes zero—has intrigued researchers since its discovery in 1911, but it took al-

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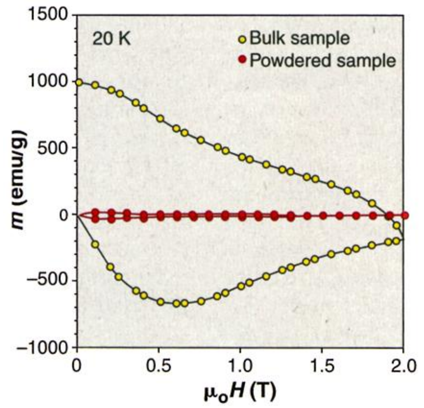
most 50 years for a microscopic theory based on the interaction between electrons and the crystal lattice to explain how such a phenomenon could exist. For real materials, these calculations are so complex that the theory cannot guide the search for new superconductors. Phenomenological theories have shown that magnetic fields in superconductors form quantized flux vortices that behave as Faraday's lines of force. However, these theories do not predict the occurrence of new superconductors, which are found by a combination of luck, serendipity, and intuition. Two main classes of practical superconductors are known today—those that exhibit their superconducting properties at very low temperatures (below 23 K) and those that will superconduct at higher temperatures (30 to 164 K). Their present applications range from the most sensitive detectors of magnetic fields ever made to large superconducting magnets used in body scanners and levitated trains.

About 40 years ago, hundreds of compounds were tested for superconductivity (*3*), but MgB_2 was missed—even though chemists had even unwittingly used this 39 K superconductor to make more complex superconductors with a T_c of less than 10 K. It may seem surprising that MgB_2 was passed over given that it is a simple material readily available from chemical suppliers. The explanation likely lies in the over 8000 possible binary compounds of the 92 elements.



Promising properties. The magnetic hysteresis loops of a bulk and a sintered sample of MgB_2 show the collapse of the hysteresis upon grinding to a powder. This indicates that the material will be easier to process than high-T_c oxide superconductors.

How does MgB_2 fit into the present range of superconducting materials? To answer this question, we must take a closer look at the properties of the two main classes of superconductors. The first comprises the low-T_c materials, which are shiny metals or slightly less shiny intermetallic compounds. The shine is not irrelevant: It indicates that their electron density is high. The standard material for superconducting magnets is NbTi, a ductile metal with a T_c of 9 K that can easily be drawn into wires. The intermetallic compound Nb_3Sn has a T_c of 18 K and is about as ductile as Wedgewood china; it might therefore seem an unlikely candidate for making kilometer-long wires, but materials scientists have devised ways of doing so and rather expensive magnets are made of this material. Josephson junctions (*4*) are normally made using pure niobium as the superconductor.

The second class comprises the high-T_c oxides, with critical temperatures above 30 K. Their discovery in 1986 caused great excitement, both because of the theoretical challenge they presented in explaining their properties and their possible applications. There is now a plethora of reasonable theories, all of which are consistent with most, but not all, experimental results. One aspect of the original microscopic theory is, however, of considerable importance: the symmetry of the wave function.

In the superconducting state, the electrons condense into a single quantum state. The fact that superconducting currents are resistanceless is no more (or less) surprising than that an electron going round an atomic nucleus does not slow down. In the superconductor, this same process is simply occurring on a much larger scale. The simplest wave function of an electron in an atom is spherically symmetric and called an "s" state. High-T_c superconductors are thought to be "d" wave superconductors, in which the amplitude of the wave function drops to zero at nodes in certain directions. This has two implications for practical purposes. First, it means that the number of normal (nonsuperconducting) electrons is higher than in an "s" wave superconductor (such as the low-T_c superconductors). Losses at microwave frequencies are therefore higher. Second, although this is not yet certain, it may be responsible for the low critical current densities across grain boundaries between crystals of different orientations in oxide superconductors. This low critical current at grain boundaries has held up the application of high-T_c superconductors.

These considerations suggest that the closer the mechanism in MgB_2 is to that of low-T_c materials, the better it is for practical applications. The report by Monteverde *et al.* (*2*) shows that at low temperatures, where the superconducting transition occurs, the resistivity is thermally activated as in a semiconductor, rather than metallic. In oxides, which are layered structures, this is the case for currents across planes, whereas the resistivity within planes is metallic. They also find that T_c depends parabolically on pressure, which is again similar to the variation in high-T_c materials. On the other hand, the variation of the penetration depth appears more "s" wave in character, and the microwave losses should thus be low. It should also be easier to make Josephson junctions with this material than with the high-T_c materials because the required sharp change from superconductor to insulator over just a few atomic layers is easier to achieve in such a simple material. The fundamental properties thus appear to be a mixture of those associated with high- and low-T_c superconductors.

However, most applications require a high current density, and this is limited in high-T_c materials by the grain boundaries. Superconductors are attractive because the high current density they can carry without heating enables high power densities. It is easier to maintain a superconducting magnet at 4.2 K than a similar copper magnet at room temperature (which would overheat), and this high power density is more important in most applications than the increase in efficiency due to zero resistance.

Magnetization curves (*5*) (see the figure) indicate that MgB_2 does not suffer from the grain boundary problem, although it is black and brittle like the high-T_c materials and therefore must have a similarly low electron density. The critical current density is proportional to the width of the hysteresis loop (*6*), and the magnetic moment is proportional to the area of the current loops. When a macroscopic sample of MgB_2 is ground up, the hysteresis loop collapses (see the figure), proving that the currents are flowing on the scale of the sample and are not small loops around each grain, as would be the case in an oxide superconductor. MgB_2 thus apparently does not need the careful alignment required in oxide superconductors and will be much easier to make into magnets.

Is MgB_2 a one-off compound or the first of a new family of superconductors? In the past, an initial major increase in the critical temperature has usually been followed by announcements of one or two materials showing substantial further increases followed by several with smaller increments with increasingly unstable and difficult materials. It is too early to tell if this will be true of MgB_2. Nevertheless, this material is unlikely to be the last surprise for scientists working on superconductors.

References and Notes

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