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10 UNSOLVED MYSTERIES IN CHEMISTRY

Many of the most profound scientific questions--and some of humanity's most urgent problems--pertain to the science of atoms and molecules

1 How Did Life Begin?

THE MOMENT WHEN the first living beings arose from inanimate matter almost four billion years ago is still shrouded in mystery. How did relatively simple molecules in the primordial broth give rise to more and more complex compounds? And how did some of those compounds begin to process energy and replicate (two of the defining characteristics of life)? At the molecular level, all of those steps are, of course, chemical reactions, which makes the question of how life began one of chemistry.

The challenge for chemists is no longer to come up with vaguely plausible scenarios, of which there are plenty. For example, researchers have speculated about minerals such as clay acting as catalysts for the formation of the first self-replicating polymers (molecules that, like DNA or proteins, are long chains of smaller units); about chemical complexity fueled by the energy of deep-sea hydrothermal vents; and about an "RNA world," in which DNA's cousin RNA--which can act as an enzyme and catalyze reactions the way proteins do--would have been a universal molecule, before DNA and proteins appeared.

No, the game is to figure out how to test these ideas in reactions coddled in the test tube. Researchers have shown, for example, that certain relatively simple chemicals can spontaneously react to form the more complex building blocks of living systems, such as amino acids and nucleotides, the basic units of DNA and RNA. In 2009 a team led by John Sutherland, now at the MRC Laboratory of Molecular Biology in Cambridge, England, was able to demonstrate the formation of nucleotides from molecules likely to have existed in the primordial broth. Other researchers have focused on the ability of some RNA strands to act as enzymes, providing evidence in support of the RNA world hypothesis. Through such steps, scientists may progressively bridge the gap from inanimate matter to self-replicating, self-sustaining systems.

Now that scientists have a better view of strange and potentially fertile environments in our solar system--the occasional flows of water on Mars, the petrochemical seas of Saturn's moon Titan, and the cold, salty oceans that seem to lurk under the ice of Jupiter's moons Europa and Ganymede--the origin of terrestrial life seems only a part of grander questions: Under what circumstances can life arise? And how widely can its chemical basis vary? That issue is made richer still by the discovery, over the past 16 years, of more than 500 extrasolar planets orbiting other stars--worlds of bewildering variety.

These discoveries have pushed chemists to broaden their imagination about the possible chemistries of life. For instance, NASA has long pursued the view that liquid water is a prerequisite, but now scientists are not so sure. How about liquid ammonia, formamide, an oily solvent like liquid methane or supercritical hydrogen on Jupiter? And why should life restrict itself to DNA, RNA and proteins? After all, several artificial chemical systems have now been made that exhibit a kind of replication from the component parts without relying on nucleic

acids. All you need, it seems, is a molecular system that can serve as a template for making a copy and then detach itself.

Looking at life on Earth, says chemist Steven Benner of the Foundation for Applied Molecular Evolution in Gainesville, Fla., "we have no way to decide whether the similarities [such as the use of DNA and proteins] reflect common ancestry or the needs of life universally." But if we retreat into saying that we have to stick with what we know, he says, "we have no fun."

2 How Do Molecules Form?

MOLECULAR STRUCTURES may be a mainstay of high school science classes, but the familiar picture of balls and sticks representing atoms and the bonds among them is largely a conventional fiction. The trouble is that scientists disagree on what a more accurate representation of molecules should look like.

In the 1920s physicists Walter Heitler and Fritz London showed how to describe a chemical bond using the equations of then nascent quantum theory, and the great American chemist Linus Pauling proposed that bonds form when the electron orbitals of different atoms overlap in space. A competing theory by Robert Mulliken and Friedrich Hund suggested that bonds are the result of atomic orbitals merging into "molecular orbitals" that extend over more than one atom. Theoretical chemistry seemed about to become a branch of physics.

Nearly 100 years later the molecular-orbital picture has become the most common one, but there is still no consensus among chemists that it is always the best way to look at molecules. The reason is that this model of molecules and all others are based on simplifying assumptions and are thus approximate, partial descriptions. In reality, a molecule is a bunch of atomic nuclei in a cloud of electrons, with opposing electrostatic forces fighting a constant tug-of-war with one another, and all components constantly moving and reshuffling. Existing mode-Is of the molecule usually try to crystallize such a dynamic entity into a static one and may capture some of its salient properties but neglect others.

Quantum theory is unable to supply a unique definition of chemical bonds that accords with the intuition of chemists whose daily business is to make and break them. There are now many ways of describing molecules as atoms joined by bonds. According to quantum chemist Dominik Marx of Ruhr University Bo-chum in Germany, pretty much all such descriptions "are useful in some cases but fail in others."

Computer simulations can now calculate the structures and properties of molecules from quantum first principles with great accuracy--as long as the number of electrons is relatively small. "Computational chemistry can be pushed to the level of utmost realism and complexity," Marx says. As a result, computer calculations can increasingly be regarded as a kind of virtual experiment that predicts the course of a reaction. Once the reaction to be simulated involves more than a few dozen electrons, however, the calculations quickly begin to overwhelm even the most powerful supercomputer, so the challenge will be to see whether the simulations can scale up--whether, for example, complicated biomolecular processes in the cell or sophisticated materials can be modeled this way.

3 How Does the Environment Influence Our Genes?

THE OLD IDEA OF BIOLOGY was that who you are is a matter of which genes you have. It is now clear that an equally important issue is which genes you use. Like all of biology, this issue has chemistry at its core.

The cells of the early embryo can develop into any tissue type. But as the embryo grows, these so-called pluripotent stem cells differentiate, acquiring specific roles (such as blood, muscle or nerve cells) that remain fixed in their progeny. The formation of the human body is a matter of chemically modifying the stem cells' chromosomes in ways that alter the arrays of genes that are turned on and off.

One of the revolutionary discoveries in research on cloning and stem cells, however, is that this modification is reversible and can be influenced by the body's experiences. Cells do not permanently disable genes during differentiation, retaining only those they need in a "ready to work" state. Rather the genes that get switched off retain a latent ability to work--to give rise to the proteins they encode--and can be reactivated, for instance, by exposure to certain chemicals taken in from the environment.

What is particularly exciting and challenging for chemists is that the control of gene activity seems to involve chemical events happening at size scales greater than those of atoms and molecules--at the so-called mesoscale--with large molecular groups and assemblies interacting. Chromatin, the mixture of DNA and proteins that makes up chromosomes, has a hierarchical structure. The double helix is wound around cylindrical particles made from proteins called histones, and this string of beads is then bundled up into higher-order structures that are poorly understood [see illustration on opposite page]. Cells exercise great control over this packing--how and where a gene is packed into chromatin may determine whether it is active or not.

Cells have specialized enzymes for reshaping chromatin structure, and these enzymes have a central role in cell differentiation. Chromatin in embryonic stem cells seems to have a much looser, open structure: as some genes fall inactive, the chromatin becomes increasingly lumpy and organized. "The chromatin seems to fix and maintain or stabilize the cells' state," says pathologist Bradley Bernstein of Massachusetts General Hospital.

What is more, such chromatin sculpting is accompanied by chemical modification of both DNA and histones. Small molecules attached to them act as labels that tell the cellular machinery to silence genes or, conversely, free them for action. This labeling is called "epigenetic" because it does not alter the information carried by the genes themselves.

The question of the extent to which mature cells can be returned to pluripotency--whether they are as good as true stem cells, which is a vital issue for their use in regenerative medicine--seems to hinge largely on how far the epigenetic marking can be reset.

It is now clear that beyond the genetic code that spells out many of the cells' key instructions, cells speak in an entirely separate chemical language of genetics--that of epigenetics. "People can have a genetic predisposition to many diseases, including cancer, but whether or not the disease manifests itself will often depend on environmental factors operating through these epigenetic pathways," says geneticist Bryan turner of the University of Birmingham in England.

4 How Does the Brain Think and Form Memories?

THE BRAIN is a chemical computer. Interactions between the neurons that form its circuitry are mediated by molecules: specifically, neurotransmitters that pass across the synapses, the contact points where one neural cell wires up to another. This chemistry of the mind is perhaps at its most impressive in the operation of memory, in which abstract principles and concepts--a telephone number, say, or an emotional association--are imprinted in states of the neural network by sustained chemical signals. How does chemistry create a memory that is both persistent and dynamic, as well as able to recall, revise and forget?

We now know parts of the answer. A cascade of biochemical processes, leading to a change in the amounts of neurotransmitter molecules in the synapse, triggers learning for habitual reflexes. But even this simple aspect of learning has short-and long-term stages. Meanwhile more complex so-called declarative memory (of people, places, and so on) has a different mechanism and location in the brain, involving the activation of a protein called the NMDA receptor on certain neurons. Blocking this receptor with drugs prevents the retention of many types of declarative memory.

Our everyday declarative memories are often encoded through a process called long-term potentiation, which involves NMDA receptors and is accompanied by an enlargement of the neuronal region that forms a synapse. As the synapse grows, so does the "strength" of its connection with neighbors--the voltage induced at the synaptic junction by arriving nerve impulses. The biochemistry of this process has been clarified in the past several years. It involves the formation of filaments within the neuron made from the protein actin--part of the basic scaffolding of the cell and the material that determines its size and shape. But that process can be undone during a short period before the change is consolidated if biochemical agents prevent the newly formed filaments from stabilizing.

Once encoded, long-term memory for both simple and complex learning is actively maintained by switching on genes that give rise to particular proteins. It now appears that this process can involve a type of molecule called a prion. Prions are proteins that can switch between two different conformations. One of the conformations is soluble, whereas the other is insoluble and acts as a catalyst to switch other molecules like it to the insoluble state, leading these molecules to aggregate. Prions were first discovered for their role in neurodegenerative conditions such as mad cow disease, but prion mechanisms have now been found to have beneficial functions, too: the formation of a prion aggregate marks a particular synapse to retain a memory.

There are still big gaps in the story of how memory works, many of which await filling with the chemical details. How, for example, is memory recalled once it has been stored? "This is a deep problem whose analysis is just beginning," says neuroscientist and Nobel laureate Eric Kandel of Columbia University.

Coming to grips with the chemistry of memory offers the enticing and controversial prospect of pharmacological enhancement. Some memory-boosting substances are already known, including sex hormones and synthetic chemicals that act on receptors for nicotine, glutamate, serotonin and other neurotransmitters. In fact, according to neurobiologist Gary Lynch of the University of California, Irvine, the complex sequence of steps leading to long-term learning and memory means that there are many potential targets for such memory drugs.

5 How Many Elements Exist?

THE PERIODIC TABLES that adorn the walls of classrooms have to be constantly revised, because the number of elements keeps growing. Using particle accelerators to crash atomic nuclei together, scientists can create new "superheavy" elements, which have more protons and neutrons in their nuclei than do the 92 or so elements found in nature. These engorged nuclei are not very stable--they decay radioactively, often within a tiny fraction of a second. But while they exist, the new synthetic elements such as seaborgium (element 106) and hassium (element 108) are like any other insofar as they have well-defined chemical properties. In dazzling experiments, researchers have investigated some of those properties in a handful of elusive seaborgium and hassium atoms during the brief instants before they fell apart.

Such studies probe not just the physical but also the conceptual limits of the periodic table: Do superheavy elements continue to display the trends and regularities in chemical behavior that make the table periodic in the first place? The answer is that some do, and some do not. In particular, such massive nuclei hold on to the atoms' innermost electrons so tightly that the electrons move at close to the speed of light. Then the effects of special relativity increase the electrons' mass and may play havoc with the quantum energy states on which their chemistry--and thus the table's periodicity--depends.

Because nuclei are thought to be stabilized by particular "magic numbers" of protons and neutrons, some researchers hope to find what they call the island of stability, a region a little beyond the current capabilities of element synthesis in which superheavies live longer. Yet is there any fundamental limit to their size? A simple calculation suggests that relativity prohibits electrons from being bound to nuclei of more than 137 protons. More sophisticated calculations defy that limit. "The periodic system will not end at 137; in fact, it will never end," insists nuclear physicist Walter Greiner of the Johann Wolfgang Goethe University Frankfurt in Germany. The experimental test of that claim remains a long way off.

6 Can Computers Be Made Out of Carbon?

COMPUTER CHIPS made out of graphene--a web of carbon atoms--could potentially be faster and more powerful than silicon-based ones. The discovery of graphene garnered the 2010 Nobel Prize in Physics, but the success of this and other forms of carbon nanotechnology might ultimately depend on chemists' ability to create structures with atomic precision.

The discovery of buckyballs--hollow, cagelike molecules made entirely of carbon atoms--in 1985 was the start of something literally much bigger. Six years later tubes of carbon atoms arranged in a chicken wire-shaped, hexagonal pattern like that in the carbon sheets of graphite made their debut. Being hollow, extremely strong and stiff, and electrically conducting, these carbon nanotubes promised applications ranging from high-strength carbon composites to tiny wires and electronic devices, miniature molecular capsules, and water-filtration membranes.

For all their promise, carbon nanotubes have not resulted in a lot of commercial applications. For instance, researchers have not been able to solve the problem of how to connect tubes into complicated electronic circuits. More recently, graphite has moved to center stage because of the discovery that it can be separated into individual chicken wire-like sheets, called graphene, that could supply the fabric for ultraminiaturized, cheap and robust electronic circuitry. The hope is that the computer industry can use narrow ribbons and networks of

graphene, made to measure with atomic precision, to build chips with better performance than silicon-based ones.

"Graphene can be patterned so that the interconnect and placement problems of carbon nanotubes are overcome," says carbon specialist Walt de Heer of the Georgia Institute of Technology. Methods such as etching, however, are too crude for patterning graphene circuits down to the single atom, de Heer points out, and as a result, he fears that graphene technology currently owes more to hype than hard science. Using the techniques of organic chemistry to build up graphene circuits from the bottom up--linking together "polyaromatic" molecules containing several hexagonal carbon rings, like little fragments of a graphene sheet-might be the key to such precise atomic-scale engineering and thus to unlocking the future of graphene electronics.

7 How Do We Tap More Solar Energy?

WITH EVERY SUNRISE comes a reminder that we currently tap only a pitiful fraction of the vast clean-energy resource that is the sun. The main problem is cost: the expense of conventional photovoltaic panels made of silicon still restricts their use. Yet life on Earth, almost all of which is ultimately solar-powered by photosynthesis, shows that solar cells do not have to be terribly efficient if, like leaves, they can be made abundantly and cheaply enough.

"One of the holy grails of solar-energy research is using sunlight to produce fuels," says Devens Gust of Arizona State University. The easiest way to make fuel from solar energy is to split water to produce hydrogen and oxygen gas. Nathan S. Lewis and his collaborators at Caltech are developing an artificial leaf that would do just that [see illustration] using silicon nanowires.

Earlier this year Daniel Nocera of the Massachusetts Institute of Technology and his co-workers unveiled a silicon-based membrane in which a cobalt-based photocatalyst does the water splitting. Nocera estimates that a gallon of water would provide enough fuel to power a home in developing countries for a day. "Our goal is to make each home its own power station," he says.

Splitting water with catalysts is still tough. "Cobalt catalysts such as the one that Nocera uses and newly discovered catalysts based on other common metals are promising," Gust says, but no one has yet found an ideal inexpensive catalyst. "We don't know how the natural photo-synthetic catalyst, which is based on four manganese atoms and a calcium atom, works," Gust adds.

Gust and his colleagues have been looking into making molecular assemblies for artificial photosynthesis that more closely mimic their biological inspiration, and his team has managed to synthesize some of the elements that could go into such an assembly. Still, a lot more work is needed on this front. Organic molecules such as the ones nature uses tend to break down quickly. Whereas plants continually produce new proteins to replace broken ones, artificial leaves do not (yet) have the full chemical-synthesis machinery of a living cell at their disposal.

8 What Is the Best Way to Make Biofuels?

INSTEAD OF MAKING FUELS by capturing the rays of the sun, how about we let plants store the sun's energy for us and then turn plant matter into fuels? Biofuels such as ethanol made from corn and biodiesel made from seeds have already found a place in the energy markets, but they threaten to displace food crops, particularly in developing countries where selling biofuels abroad can be more lucrative than feeding people at home. The numbers are daunting: meeting current oil demand would mean requisitioning huge areas of arable land.

Turning food into energy, then, may not be the best approach. One answer could be to exploit other, less vital forms of biomass. The U.S. produces enough agricultural and forest residue to supply nearly a third of the annual consumption of gasoline and diesel for transportation.

Converting this low-grade biomass into fuel requires breaking down hardy molecules such as lignin and cellulose, the main building blocks of plants. Chemists already know how to do that, but the existing methods tend to be too expensive, inefficient or difficult to scale up for the enormous quantities of fuel that the economy needs.

One of the challenges of breaking down lignin--cracking open the carbon-oxygen bonds that link "aromatic," or benzene-type, rings of carbon atoms--was recently met by John Hartwig and Alexey Sergeev, both at the University of Illinois. They found a nickel-based catalyst able to do it. Hartwig points out that if biomass is to supply nonfossil-fuel chemical feedstocks as well as fuels, chemists will also need to extract aromatic compounds (those having a backbone of aromatic rings) from it. Lignin is the only major potential source of such aromatics in biomass.

To be practical, such conversion of biomass will, moreover, need to work with mostly solid biomass and convert it into liquid fuels for easy transportation along pipelines. Liquefaction would need to happen on-site, where the plant is harvested. One of the difficulties for catalytic conversion is the extreme impurity of the raw material--classical chemical synthesis does not usually deal with messy materials such as wood. "There's no consensus on how all this will be done in the end," Hartwig says. What is certain is that an awful lot of any solution lies with the chemistry, especially with finding the right catalysts. "Almost every industrial reaction on a large scale has a catalyst associated" with it. Hartwig points out.

9 Can We Devise New Ways to Create Drugs?

THE CORE BUSINESS of chemistry is a practical, creative one: making molecules, a key to creating everything from new materials to new antibiotics that can outstrip the rise of resistant bacteria.

In the 1990s one big hope was combinatorial chemistry, in which thousands of new molecules arc made by a random assembly of building blocks and then screened to identify those that do a job well. Once hailed as the future of medicinal chemistry, "combi-chem" fell from favor because it produced little of any use.

But combinatorial chemistry could enjoy a brighter second phase. It seems likely to work only if you can make a wide enough range of molecules and find good ways of picking out the minuscule amounts of successful ones. Biotechnology might help here--for example, each molecule could be linked to a DNA-based "bar code" that both identifies it and aids its extraction. Or researchers can progressively refine the library of candidate molecules by using

a kind of Darwinian evolution in the test tube. They can encode potential protein-based drug molecules in DNA and then use error-prone replication to generate new variants of the successful ones, thereby finding improvements with each round of replication and selection.

Other new techniques draw on nature's mastery at uniting molecular fragments in prescribed arrangements. Proteins, for example, have a precise sequence of amino acids because that sequence is spelled out by the genes that encode the proteins. Using this model, future chemists might program molecules to assemble autonomously. The approach has the advantage of being "green" in that it reduces the unwanted by-products typical of traditional chemical manufacturing and the associated waste of energy and materials.

David Liu of Harvard University and his co-workers are pursuing this approach. They tagged the building blocks with short DNA strands that program the linker's structure. They also created a molecule that walks along that DNA, reading its codes and sequentially attaching small molecules to the building block to make the linker--a process analogous to protein synthesis in cells. Liu's method could be a handy way to tailor new drugs. "Many molecular life scientists believe that macromolecules will play an increasingly central, if not dominant, role in the future of therapeutics," Liu says.

10 Can We Continuously Monitor Our Own Chemistry?

INCREASINGLY, chemists do not want to just make molecules but also to communicate with them: to make chemistry an information technology that will interface with anything from living cells to conventional computers and fiber-optic telecommunications.

In part, it is an old idea: biosensors in which chemical reactions are used to report on concentrations of glucose in the blood date back to the 1960s, although only recently has their use for monitoring diabetes been cheap, portable and widespread. Chemical sensing could have countless applications--to detect contaminants in food and water at very low concentrations, for instance, or to monitor pollutants and trace gases present in the atmosphere. Faster, cheaper, more sensitive and more ubiquitous chemical sensing would yield progress in all of those areas.

It is in biomedicine, though, that new kinds of chemical sensors would have the most dramatic potential. For instance, some of the products of cancer genes circulate in the bloodstream long before the condition becomes apparent to regular clinical tests. Detecting these chemicals early might make prognoses more timely and accurate. Rapid genomic profiling would enable drug regimens to be tailored to individual patients, thereby reducing risks of side effects and allowing some medicines to be used that today are hampered by their dangers to a genetic minority.

Some chemists foresee continuous, unobtrusive monitoring of all manner of biochemical markers of health and disease, perhaps providing real-time information to surgeons during operations or to automated systems for delivering remedial drug treatments. This futuristic vision depends on developing chemical methods for selectively sensing particular substances and signaling about them even when the targets occur in only very low concentrations.