not important," he says. Competition between males may be more important in evolution, driving the development of larger canines or body sizes in male primates. Or, the competition among males could be at the level of the sperm, says Harvey: "Let all the sperm compete, thereby having male offspring whose sperm will also be good."

Others say that females may be making choices but hiding them: Blaffer Hrdy has proposed that females who mate with many males might be trying to make them all think that the subsequent offspring are theirs: "By drawing several different males into the web of possible paternity, females may increase the likelihood of male protection and even care (of their infants)." And there may be entirely different but equally important factors driving their mating behavior and complicating the picture of female choice in primates. Oxford University zoologist William D. Hamilton speculates that the reason primates spend so much time inspecting rear ends before mating may be that they are checking to see if their prospective mate is carrying a contagious virus.

All that's speculation, however, and other researchers say that the only way to really see if female choice is having an evolutionary impact is through definitive paternity studies. Trivers says such studies are needed to determine whether females are favoring certain males at the peak of their estrus, when they ovulate. Smuts agrees: "We have no direct information on the consequences of female choice until, first of all, we know who actually fathered their offspring. The Barbary macaque may mate with 30 different males, but only one is the actual father."

Those paternity studies have been done in lemurs and in a few other species, but primatologists are just beginning to overcome problems with contamination of DNA samples and are setting up collaborations with molecular biologists so that they can use the method to sort out the complex behavior of primates in the wild. Until those studies are done, however, the evolutionary consequences of female mate choice in primates will remain a puzzle. In the end, it may be that female choice theory doesn't transfer from birds to primates. "What's going on in many birds may be simpler and more straightforward than behavior in primates," says Smuts. But, then, maybe that shouldn't be so surprising if one considers the behavior of that other primate species—humans: "If you took a broad sample of women in our society, looking at who they were dating and mating with, you'd see tremendous variety. If you tried to come up with a single theory, say about women going with men who have money, you wouldn't get very far. I think nonhuman primates are just as complex and subtle on a social level as we are."

–Ann Gibbons

MOLECULAR DESIGN

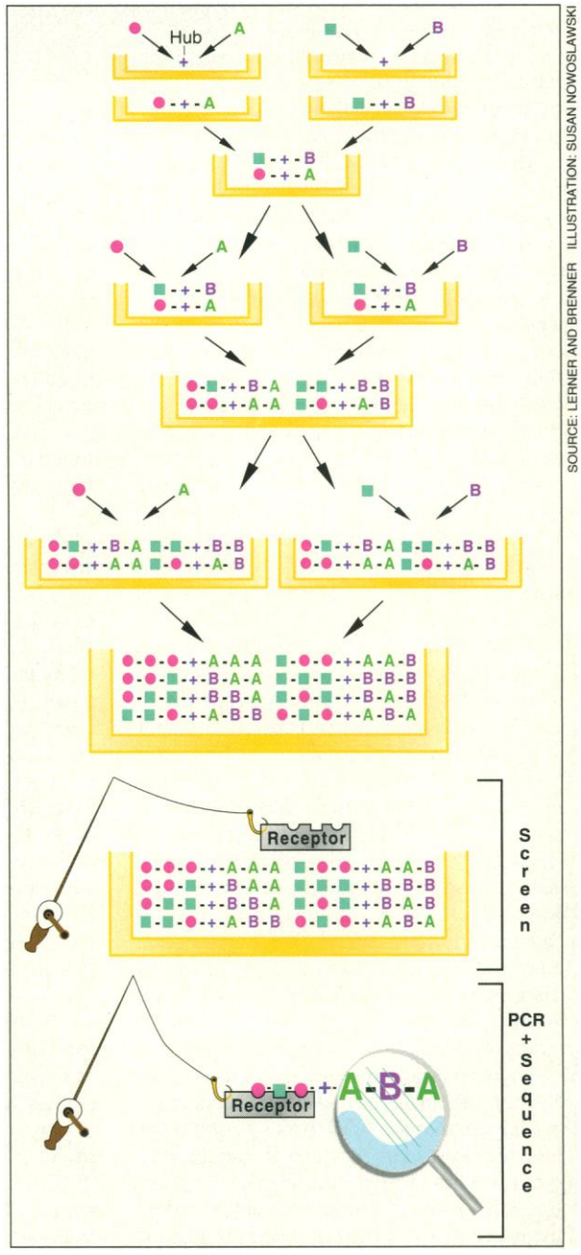
Speeding Up a Chemical Game of Chance

To hang a reality check on the optimistic buzz phrase "rational drug design," molecular biologist Sydney Brenner of Cambridge University titles one of his stock lectures "Irrational Drug Design." Sure, designing a specific molecule for a specific research or medical job is a nice idea whose day probably will come, Brenner says. But making molecules to measure requires knowing the exact shape, size, and chemical characteristics of the environment in which it will function—and such knowledge is usually lacking. In most cases, concludes Brenner, good old trial and error is hard to beat. Too bad: It can cost drug makers more than a decade of research effort and hundreds of millions of dollars before it lands them a product. But Brenner and his chemist colleague Richard Lerner, president of the Scripps Research Institute in La Jolla, California, believe they have a way to cut time and costs: They have set out to make a Ferrari of trial and error methods. Call it rational trial and error.

In the 14 June *Proceedings of the National Academy of Sciences*, Brenner and Lerner unveil what they call encoded combinatorial chemistry. Though the scheme has yet to be tested, chemist Steven Ramcharitar has already worked out its technical basics in Kim Janda's laboratory at Scripps, and the concept itself is dazzling other chemists. Says synthetic chemist Samuel Danishefsky of Yale University, who uses traditional methods to build organic molecules: "It's absolutely ingenious."

Lerner and Brenner have stepped into a fast-growing field. Like other researchers trying to speed up drug design, they hope to turn the laborious process of testing molecules one by one into a more efficient talent search, in which tens of thousands of molecules would be created and screened en masse. That raises a dual challenge: how to mix a limited palette of components such as amino acids efficiently to create a broad array of variants, and how to track down those few variants that show promise, even if they are present in vanishing quantities. By uniting the molecule-making talents of synthetic chemistry with the record-keeping abilities of DNA, Brenner and Lerner's method promises to solve both problems at once.

To spawn a horde of variants, Lerner and Brenner propose a novel way to link a few different building blocks, or monomers—



Mix and match. A strategy for linking amino acids *(shapes)* and nucleotides *(letters)* creates a combinatorial explosion of peptides, each with an easy-to-read DNA label.

amino acids, say—into virtually every combination that is chemically and mathematically possible. The molecule-making might begin with a mixture of 20 amino acids, each one hooked to a kind of molecular hub that allows the chain to grow in only one direction. The mixture would then be divided into 20 batches, and the 20 amino acids would be added again, one to each batch, to create short peptides (amino acid chains) containing all possible two-monomer combinations. The molecule makers would then pool the peptides, redivide them, and add a third monomer to each batch. By cycling through these steps just four times using the 20 amino acids, researchers could create 160,000 tetrapeptides in the space of a day.

But once the molecules are in hand, how do you fish out the good eggs from the bad and the boring? Brenner and Lerner plan to test their compounds for activity by exposing them to biological receptors such as antibodies. But such tests capture only the tiniest amount of the desired compound, probably too little for chemical analysis. And with tens of thousands of molecules in the mixture, how can Brenner and Lerner know which of them fitted the bill? Their strategy is to give each variant an easy-to-read label.

The ideal molecular label, the researchers decided, would be made of DNA. Lerner explains that the tools of biotechnology make it easy to "read" a trace amount of unknown DNA: Simply amplify the sequence—multiply it millions of times—via the polymerase chain reaction (PCR), then sequence it. To create their PCR-able labels, the researchers devised their own genetic code by assigning a specific genetic tag to each of their monomers. Then, each time they add another monomer to a batch of growing peptides, they will also add the corresponding tag. Successive tags should link end to end to form a DNA chain, attached to the hub.

The molecular complexes emerging from the combinatorial process will thus carry a peptide on one side—and a long-winded DNA label at the other. Amplifying and sequencing the label of any peptide fished out during the screening should give the researchers a clear chemical road map for making larger quantities of the substance.

So far, Janda says, he and Ramcharitar have verified the basic chemistry of the technique by constructing an eight-member peptide along with its genetic tag, which they have successfully amplified and sequenced. "Now we are starting to work on making a [peptide] library," Janda adds.

Once proven, Brenner and Lerner's scheme for creating and tracking molecular variants will have to contend with some rivals in what combinatorial chemist Stephen Fodor calls "a fantastic and growing field." Fodor, head of physical sciences at the Affymax Research Institute, a 3-year-old biotechnology company in Palo Alto, should know. In the 15 February 1991 *Science*, he and his colleagues described their strategy for creating thousands of different peptides, each one occupying its own microterritory within an area the size of a postage stamp. After coating a glass slide with a particular amino acid, the researchers use a photographic mask to illuminate specific regions of the slide, linking a second amino acid to the underlying one via a light-driven reaction. Changing the pattern of illumination while adding each successive amino acid yields, in principle, as many as 65,000 different peptides, laid out in a spatial array.

As in Brenner and Lerner's technique, each peptide's identity is easy to trace—although in this case the clue is location rather than a genetic tag. Affymax's strategy is restricted to chemical assembly processes that can be driven by light. But Fodor maintains that "in the big picture, all of these combinatorial methods will have their right applications."

So will traditional techniques for making and trying out new molecules one by one, as Yale's Danishefsky points out. "I don't find [combinatorial strategies] at all threatening to synthetic organic chemistry." For one thing, he explains, the new methods yield linear, chainlike polymers; they appear unsuited for making the more complex, multiringed structures of many biologically active molecules, including steroids. And getting the molecular chains to grow according to plan takes plenty of clever synthetic chemistry. But "right now," says Lerner, "if you want to discover useful molecules, combinatorial chemistry is a pragmatic way to go."

–Ivan Amato

ASTRONOMY

Black Holes: A New Heavyweight Champ

For objects that are by definition invisible, black holes have been making quite a show lately. Small black holes may be to blame for the peculiar bursts of x-rays coming from some binary stars (*Science*, 14 February, p. 794); much larger ones, weighing millions of times as much as the sun, seem to marshal the throngs of stars at the centers of several nearby galaxies. Now, John Kormendy of the University of Hawaii and Douglas Richstone of the University of Michigan report strong evidence for a behemoth weighing in at perhaps a billion times the mass of the sun, at the heart of another neighboring galaxy.

The discovery, reported last Friday in *The Astrophysical Journal*, doesn't just set a new benchmark in a contest of size. The black hole, if it's there, is also the best candidate yet for being the corpse of a quasar, a brilliant beacon that burned when the universe was young. Some quasars are still visible today at the far fringes of the universe, and for most astronomers the only plausible explanation of their titanic energy output is the gravitational pull of a black hole of perhaps a billion solar masses, sucking in material at the center of a newborn galaxy. As the galaxy ages and its supply of gas and dust dwindles, the quasar should flicker out. If so, billion-solar-mass black holes should lurk, dormant, at the centers of many otherwise ordinary galaxies. With this latest discovery, says Kormendy, "we're finding what we should be finding."

Hints of such quasar-sized black holes are nothing new. Kormendy reported signs of one in the so-called Sombrero galaxy in 1988. And early this year Space Telescope scientists released dramatic images of a galaxy called M87 showing stars drawn into a tight knot at the center, presumably by an enormous central mass. But the earlier evidence was circumstantial, say Kormendy and one of the Space Telescope scientists, Sandra Faber of the Lick Observatory. In this latest case, says black-hole hunter John Tonry of the Massachusetts Institute of Technology, "They have a very clear signature...It's implausible that it's anything else."

What makes the case so convincing is Kormendy and Richstone's detailed picture of how stars are moving in the core of the galaxy, NGC 3115. They gathered light from its innermost 300 light-years with the 3.6-meter Canada-France-Hawaii telescope on Mauna Kea, then passed it through a spectrograph, which can serve as a kind of celestial police radar. Doppler shifts in the spectral lines revealed how fast the stars are whirling around the center of the galaxy—and they showed that the speed increases dramatically toward the very center.

Assuming the core of the galaxy is not on the verge of flying apart, an enormous amount of mass has to be holding the whirling stars in place—over 10 times more than is visible, even though stars are densely clumped near the center. The hidden mass amounts to a billion times that of the sun, the researchers calculate, and they believe a black hole is the only plausible explanation.

Tonry, Kormendy, and Richstone, who was working with Alan Dressler of the Carnegie Institution of Washington, have already traced less frenetic versions of this stardance in two other galaxies, M31 and M32, suggesting that they host smaller black holes of several million solar masses. And this new find may not hold the record for long. The evidence in NGC 3115 emerged from a survey of 15 nearby galaxies. Several other galaxies in Kormendy and Richstone's sample are looking promising, says Kormendy, including one that "could be right up there with the best."

–Tim Appenzeller