signal will circle all the way around the damaged tissue and end up back where it began, starting the cycle all over again, and going around and around and around, several times a second. This creates a rotating cycle of contractions in the heart that resembles fans at a football game doing "the wave." A person whose heart is doing "the wave" will have a very fast heartbeat: tachycardia.

Winfree's model implies that the heart does not need damage for a rotating wave to form. Several recent experiments have confirmed this. Jose Jalife at the State University of New York Health Sciences Center in Syracuse experimented on a 2-centimeter-square layer of sheep heart muscle kept alive in a tissue bath. With collaborators Jorge Davidenko, Paul Kent, Dante Chialvo, and Donald Michaels, Jalife used electrodes on two sides of the heart tissue to apply two stimuli timed according to Winfree's predictions. The result was spiral waves in perfectly healthy tissue, Jalife says.

More striking is a double rotating wave produced in Raymond Ideker's lab at Duke University Medical School in an intact dog heart. Ideker and student Nitaro Shibata applied two timed electrical stimuli in line with Winfree's predictions and produced two separate waves of electrical activity circling two pivot points on the heart (see figure).

What does this have to do with tachycardia in human hearts that don't get two carefully timed electrical stimuli? The connection isn't clear, Winfree admits, but the ability of healthy heart tissue to sustain rotating waves is important for several reasons. One is that it provides a simple model for studying rotating waves—one that doesn't involve damaged tissue. Second, the results indicate that it's possible tachycardia can be triggered in healthy hearts by some stimulus that has a similar effect to the electrical shocks in the lab experiments. "There are mechanisms galore that you can imagine in your armchair," Winfree says. If healthy hearts are vulnerable to tachycardia, cardiologists would want to know.

Perhaps the major implications in Winfree's rotating wave model, however, involve understanding the onset of fibrillation, which in human hearts often starts with a period of rapid heartbeat. And in the laboratory models in which tachycardia is induced by electrical stimulation, exactly the same thing happens. "The first rotating wave takes 140 or 160 milliseconds; the second one takes 120 or 140," Winfree says. "When the period gets down to less than 100 milliseconds, the waves are coming faster than the tissue can respond, and it deteriorates into fibrillation."

Such models as Winfree's provide a base line from which experimental cardiologists can study not only the normal heart but also hearts that have been damaged in a specific way. At the University of Limberg in the Netherlands, for example, Maurits Allessie has tested rabbit hearts in which he mimics the effects of muscle damage by freezing part of the heart. In cases where an entire area is killed except for the top 1 millimeter, Allessie finds that although he can induce tachycardia in the heart, he cannot push it into fibrillation. Discovering why a heart that has been damaged in this way will not fibrillate could provide insight into preventing fibrillation in humans.

At Columbia University in New York City, Andrew Wit studies rotating waves in animal hearts where a major coronary artery has been tied off to imitate the damage caused by a coronary blockage in humans. Just like humans, the animals suffer from ventricular tachycardia in the first week after their "heart attack," and just like in humans the rotating waves of tachycardia can lead to fibrillation. Wit has found that the causes of the later episodes of tachycardia are different from what triggers them right after the heart attack and that the anatomy of the surviving cells is important in determining whether an animal will have problems. He hopes eventually to develop drugs that can prevent the rotating waves from developing.

But his models tell Winfree more than what can cause a potentially fatal bout of fibrillation; they also suggest ways to improve the designs of contemporary pacemakers. Winfree calculates that the best electrodes for pacemakers would be spheres with a radius of about a quarter of a millimeter, much smaller that the size of those now in use. And, he says, current pacemakers probably use more energy than necessary, thus shortening battery life and increasing the risk of damage to heart tissue. "The theoretical calculations imply that if you make the electrode the right shape and size you can reduce the energy needed by a factor of 10," he says.

The potential for improving defibrillators is even greater, Winfree says. "What we do today [with defibrillators] will someday be considered as crude as trepanning," he predicts, referring to the ancient practice of removing a piece of the skull to let evil spirits out. The electrical jolt of a defibrillator damages the heart, often so badly that a patient whose heart starts back up will die of a second fibrillation a few hours later. The energy requirement could probably be reduced by a factor of 10 or even 100, and do the same job with much less damage, Winfree says.

Ultimately, heart researchers would like to build a device that can continuously monitor a heart's electrical activity, decide when the heart is getting dangerously out of its normal pattern, and apply the proper electrical stimulus to set it right. Although there are experimental devices now that try to do such a job, truly effective units will have to wait until researchers have a better quantitative understanding of the electrical rhythms of the heart. But once that happens, the Hank Gatherses of the future should be able to play their games without the fear that their hearts will betray them.

■ ROBERT POOL

Tweaking Molecules with Laser Light

When Keith Nelson talks about his "molecular tweezers" he doesn't mean he has a tiny tool that can physically grip a molecule and move it. But he does have the next best thing. Nelson, a chemist at the Massachusetts Institute of Technology, is part of a group of researchers that has for the first time harnessed sequences of laser pulses to push molecules around. The technique opens the way to studying molecules in configurations other than their equilibrium states, something chemists must do if they are to understand intermediate states in chemical reactions. In the future, precisely controlled laser pulses might even be used to drive chemical reactions or phase transitions in crystals.

The dream of controlling molecules with laser light goes back to the early 1960s, when lasers first became laboratory tools. One early idea was to use lasers as "molecular scissors." Since each chemical bond in a molecule has its own characteristic energies, researchers hoped that by tuning lasers to match those energies, they could put enough energy into the bond to distort it or even break it altogether. Over two decades, researchers spent a great deal of time and money pursuing this Holy Grail, to no avail. "By the mid-1980s," says Herschel Rabitz, a theoretical chemist at Princeton University, "people had decided it was an impossible problem." The difficulty is that molecules tend to redistribute the energy they absorb among many chemical bonds, making the "scissors" too blunt to do the job.

Nelson, along with MIT chemist Gary Wiederrecht and Bell Communications Research laser specialists Andrew Weiner and Dan Leaird, took a different approach in their laser experiments. As they report on page 1317, they were not trying to create a

reaction but simply wanted to move molecules inside a crystal and then examine them in their new configuration. In earlier work, other researchers had produced molecular movements with relatively long, single pulses of light. But because such movements take place on a time scale of femtoseconds (10^{-15} second), the workers were not able to examine the details of the motion their lasers induced.

So Nelson and his colleagues recognized that they would have to employ pulses not much longer than femtoseconds. But they also knew that single pulses that are too short can't be selective and will push molecules in several directions at once.

In the MIT/Bellcore work, the researchers exposed a crystal of the organic molecule perylene to a sequence of 75-femtosecond-long laser pulses, timed to 400-femtosecond intervals. That frequency matches the natural frequency of a particular vibration of the crystal in which pairs of molecules move together and apart. Pushing the molecules with a sequence of laser pulses is similar, Nelson says, to propelling a child on a swing by giving the swing a shove each time it reaches its bottom point. The technical difficulty in the experiment, he says, was controlling the laser to produce a dozen incredibly short pulses at precise intervals.

The sequence of pulses moved the perylene molecules less than 0.001 angstrom. That is not very far, Nelson admits, but it is a first step. Eventually, he believes, it will be possible to move molecules by more than 0.1 angstrom with this technique.

Such advances will require improvements in the control of femtosecond lasers as well as a better understanding of molecular dynamics, Rabitz says. The MIT/Bellcore group chose a system that was fairly easy to manipulate, he notes—a crystalline structure limits the types of motion a molecule can undergo. But to "make molecules dance to our tune" will require careful design of the laser input, he says. Chemists trying to use laser pulses to move molecules in precise ways face much the same problem as engineers planning a careful sequence of rocket firings to orient a space station properly, Rabitz says. But the molecular work is even harder because molecules are not rigid and they respond in a much more complicated way to outside pushes.

Still, Rabitz says, the recent development is an important first step. Nelson is more excited. "In the 1980s we saw a revolution in our ability to watch elementary chemical motion [with femtosecond lasers]," he says. "The 1990s will see a similar revolution in our ability to manipulate molecular motion, including motion that leads to chemical or structural change." ■ **ROBERT POOL**

CF Screening Delayed for Awhile, Perhaps Forever

Efforts to develop a test to detect those who carry the cystic fibrosis gene have hit an unexpected roadblock

JUST AS THE MEDICAL COMMUNITY had begun planning for what promises to be the biggest genetic screening program to date—to detect people who carry the abnormal cystic fibrosis gene—new scientific evidence suggests that such a screening program may not be feasible after all, or at least not as quickly as anyone imagined.

The depressing news emerged last week as a panel of geneticists, physicians, genetic counselors, and lawyers met at the National Institutes of Health to craft guidelines to usher cystic fibrosis screening into routine medical practice. But they quickly hit an unexpected roadblock.

It turns out that the cystic fibrosis mutations are far more complex than anyone anticipated. Last summer, when Lap-Chee Tsui of the Hospital for Sick Children in Toronto and Francis Collins of the University of Michigan Medical School found the gene, they identified a simple mutation in it that causes most cases of the disease. About 75% of those who carry the abnormal gene have this particular mutation. The rest have other mutations in the same gene.

Foiled for now. *Arthur Beaudet and other geneticists hope their cystic fibrosis test problems are temporary.*

Almost as soon as the gene was cloned, a handful of biotechnology companies began offering a DNA test to detect this particular mutation. And a more accurate test seemed just around the corner, once the other mutations, expected to number about a dozen, were identified. In a collaborative effort coordinated by Tsui, nearly 70 labs around the world set out to find those mutations. They predicted they would have them—and thus a definitive test—within a year.

But optimism faded last week when Tsui reported that instead of a few common mutations, the investigators have so far turned up more than 20 rare ones. Together, they account for no more than a few percent of the remaining mutations. In fact, most are "private" mutations that occur in just one individual. "These findings bode ill," says Collins. He suspects that there are lots of ways "to mutate this gene to get cystic fibrosis. It is a big gene, and a big target for abnormalities."

Of course, all that could change tomorrow; someone could find one or two much more common mutations, says Arthur Beaudet, a geneticist at Baylor College of Medicine and cochair of the workshop. After all, the researchers have searched through only 10 or 20% of the gene's coding regions, mostly around the site where the first mutation was found. But he and the other assembled scientists agreed with Collins, who professed to a sinking feeling that "we could be here a long time"—and in the worst scenario, forever.

The biggest fear is that once 30, 40, or even hundreds of mutations have been found, 10 or 15% may still be unaccounted for, says Haig Kazazian, a geneticist at Johns Hopkins University School of Medicine who chaired the meeting along with Beaudet. And there is ample precedent for this scenario, Kazazian says: in many of the disorders linked to the X chromosome, including Duchenne muscular dystrophy and hemophilia A, "practically every unrelated person has a different mutation." If that is true for cystic fibrosis, then designing an accurate, cheap, and simple test, with today's technology, is a near impossibility, says Kazazian.

All of which makes the question of whether and when to implement widespread genetic screening even knottier than everyone already thought it was (see *Science*, 5 January, p. 17). The group agreed that for now widespread screening is premature, as the existing test would detect just 75% of the carriers, and thus only half of the couples at risk of having a child with cystic fibrosis. They recommended the test only for those with a family history of the disease.