

From High-Energy Physics to Medical Research . . . It Happens

by Emlyn Willard Hughes

Polarized ^3He (one neutron and two protons with opposite spins) has provided insights into the insides of a neutron and the insides of a human lung. In the neutron experiment at SLAC, about a liter of ^3He was polarized by high-powered lasers in the glass cell in the center of the target at left, which was then bombarded by electrons at energies of 50 billion electron volts. The steel coils surrounding the cell provide the magnetic field to control the spins. The target now leads a quieter life at Caltech, where it's dedicated to polarizing noble gases for medical imaging.

Research in fundamental science often spins off technological innovations. My story here is about an especially unusual spin-off, because it's so dramatically different from what we originally set out to do. I'm an experimental high-energy nuclear physicist, so first I'm going to torture you with a few details of our physics experiment, and then I'll go on to the spin-off, which landed us in biomedical engineering.

I'll start with the basics: the periodic table of the elements. If you survived as an undergraduate, certainly as one at Caltech, you battled with this in many different courses, and you probably know it in your sleep. You know its structure and how it all adds up. You know that electrons (and other particles) have spin and that Pauli's exclusion principle, which states that no two electrons with the same spin can occupy the same state, is the underpinning of the periodic table and explains the great variety in the structure of the elements. And you might know why the electron in a hydrogen atom doesn't collide with its proton, even though they are oppositely charged.

But even if you understand all of this, you probably cannot answer the simple, basic question underlying the periodic table: why does a proton stick to a proton? The protons are both positively charged, so certainly it isn't an electromagnetic interaction, but *something* is holding these two things together. A comparable question that is equally puzzling is, why does a proton stick to a neutron? These are reasonable questions if you want to understand the periodic table and how nuclei get to be nuclei. You might have smart kids who will come and ask you this someday. If you ask Caltech's provost, who is a nuclear physicist, you're going to hear things like field theory, the nuclear shell model, and other incredibly complicated stuff, but ultimately you will get the impression that perhaps we don't really know how to answer this question. That's why I spent 10 years of my life in nuclear physics trying to figure it out.

The first mental leap from those questions is this: if you want to understand how protons stick together, you probably should understand what's inside them and how the proton works. So let's look at what we know about the proton.

It's pretty simple in some ways. It has a charge of one and a spin of one half. We know that it has a mass of 938 million electron volts (MeV), and we know that it's a very stable particle. It has a lifetime much greater than the age of the universe—on the order of 10^{25} years, with even the most pessimistic measurements.

The neutron is very similar. It has a charge of zero and a spin of one half. It's a little bit heavier than the proton—939.6 MeV. One of the big differences between the proton and the neutron is its lifetime—a free neutron lasts only for about 15 minutes before decaying into a proton, an electron, and a neutrino. It's very stable when embedded in a nucleus, but it's difficult to study as a free neutron, because it won't stay around very long.

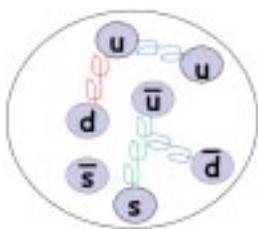
Our high-energy experiments to look inside these particles involved scattering an electron off either a proton or a neutron, so we had to create the proton and neutron targets. Now, proton targets are easy—you just use hydrogen (you can distinguish between the electron and proton in the scattering process). But for neutron targets, we had to use nuclei, because you can't produce a free-neutron target.

The proton, however, has a very complicated internal structure. We believe we understand *what* is inside the proton, but understanding its behavior is the difficult part. From the view of high-energy physics, the proton is not a fundamental particle. It's made up of smaller constituents—quarks and gluons—that we believe are fundamental, at least today. Quarks are the particles inside the proton, and gluons the mediators that cause the interaction between the quarks. It's complicated because the quarks come in different types, or "flavors"—up, down, anti-up, strange,

charm, and so on. And the gluons aren't simple either; they have different "colors," and their interaction is a complex process as well. But this is what we've got to deal with if we want to understand how a proton works.

When you start trying to figure out something like this, you choose some particular question to answer. In the early 1990s, physicists had already looked quite a bit at what carries the mass of the proton and neutron, so the next question was: what carries the spin? Since protons and neutrons are made up of quarks and gluons, the problem became one of measuring how much quarks contribute to the spin versus how much of it comes from gluons. A somewhat crude measurement made at CERN (the European Organization for Nuclear Research) in Geneva found that the quark's contribution to the proton's spin was small. This launched experimental efforts all over the world to measure more precisely what the total quark contribution to the proton's spin would be. And this is where I came into it.

If you want to see inside the proton and neutron, you need to use a simpler particle like an electron, which we believe has no internal structure. You have to accelerate this electron to very high energies and then scatter it off the protons and neutrons, looking at the results in a detector. Because we wanted to understand something about spin, we had to do spin-dependent scattering. That meant that we had to control the spin of the electrons as well as the spin of the protons and neutrons. Our experiments scattered electrons with a particular spin off protons with a particular spin. The scattered electrons' spins were then parallel or antiparallel to the target's spin, and we performed an asymmetry measurement, counting the electrons we detected while keeping track of their spin.



Above: Inside the proton are quarks that come in different "flavors"—up, down, anti-up, strange, and so on—and gluons, which mediate the interaction between the quarks and occur in different "colors."

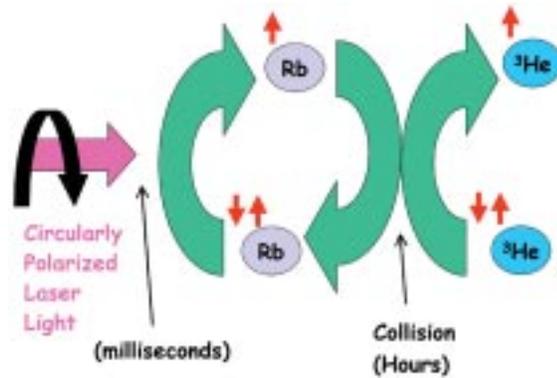
Below: The accelerator at the Stanford Linear Accelerator Center stretches for two miles, crossing Highway 280.



To get the energies we want for our experiment, we need a very high-energy electron machine. We have one in Northern California—SLAC (the Stanford Linear Accelerator Center), which is two miles long and crosses underneath Highway 280 about half way between San Francisco and San Jose. SLAC produces electrons at energies of 50 billion electron volts and, at the end of the two mile run, flings them into a big experimental hall about the size of a football field, where we scatter them off various proton and neutron targets. The hall has to be huge because these collisions produce intense radiation, so all the equipment is heavily shielded.

For our neutron target at SLAC (remember, you have to use a nucleus, because free neutrons decay so fast that you might as well forget about controlling their spin), we used the nucleus embedded in polarized helium, specifically helium-3, or ^3He . Now, ^3He is just like ^4He : it doesn't decay radioactively, and it's a noble gas, which means it's inert and doesn't react with anything. The only difference is that ^3He has one less neutron. If you control, or polarize, the nuclear spins of ^3He , the two proton spins end up antiparallel to each other, due to the Pauli exclusion principle. These paired spins are effectively invisible, so if you scatter electrons off ^3He and you observe spin-dependent scattering, it has to have come from the neutron.

Our first problem was how to polarize the ^3He . We used a rather complex atomic physics method that basically consisted of mixing a bottle of ^3He with rubidium. If you heat up the rubidium, it produces a small amount of vapor, and you can use circularly polarized laser light to polarize rubidium atoms in the vapor. It takes a few milliseconds to polarize rubidium. Then, if the rubidium, which is now spin-up, collides with a spin-up helium atom, nothing happens. They both remain spin-up. But if this rubidium atom collides with a helium atom that's spin-down, then the two actually reverse spin, the rubidium



To polarize ^3He , you hit a rubidium atom with circularly polarized laser light, giving the atom spin up. When that atom collides with a spin-down helium atom, they reverse spin, but the rubidium immediately gets repolarized to spin up again and ready to change the spin of another helium atom. The first part of the process is very fast, but keeping it going long enough to obtain a liter of 50-percent polarized spin-up helium demands patience.

becoming spin-down and the helium spin-up. The spin-down rubidium quickly (milliseconds, again) gets repolarized by the laser, so, from the point of view of the ^3He atoms, they're always seeing spin-up rubidium. The ^3He -Rb interaction is weak; it takes hours to polarize the ^3He , but you can get to very high values—50-percent polarization—if you're patient enough to let it build up. We needed about a liter of ^3He for our target, which took 24 hours to polarize. Building it was a large, multimillion-dollar technical project, because it included all the equipment to polarize ^3He inside it. (When our experiment was over, SLAC didn't care about our target anymore, so I swiped it and brought it to Caltech, including all the polarizing lasers.)

I'll leave the experiment now and jump quickly to the results. We published a short paper in *Physical Review Letters* and later a longer article in *Physical Review D*, both with 48 authors. When you publish a high-energy physics experiment, you never get to see your first name; the most you can expect is your initials. You'll see the relevance of this later, when I move over to the medical side.

Over a 10-year period, start to finish, including building the target, we measured the quark contributions to the one-half spin of the neutron to be about 0.1—i.e., 20 percent of the spin, which is pretty small. We measured it to within an error of about ± 0.05 , which is quite a respectable level of accuracy.

We were not, however, able to measure the gluons very well. We found an upper limit on the gluon contribution to the spin of 1.7 ± 1 . That's a gigantic error bar, so it's basically a non-measurement. We knew this going in, because the gluon measurement needs a much higher energy than SLAC can provide. You need to smash two beams head-on in a collider, because the center-of-mass energy is the sum of the energies in the two beams. In a fixed-target experiment like SLAC, you have only the energy from the electron beam. Such a collider does exist at DESY in Hamburg, Germany—a machine that can take a 900-billion-electron-volt proton and collide it with a 30-billion-electron-volt electron. But measuring the gluons is at least a decade away, because, although we know how to control the spin of the electron,

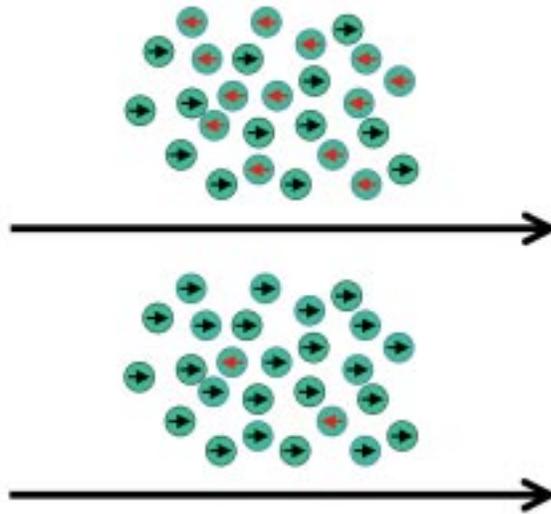
Embedded in the middle of a block of coauthors, "E.W. Hughes" hardly stands out. And there's only room for initials.

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Deep inelastic scattering of polarized electrons by polarized ^3He and the study of the neutron spin structure

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Atoms in a magnetic field (top) align their spins with or against the direction of the magnetic field (arrow). The signal in an MRI scan comes from the tiny excess of water atoms aligned with the field. Hyperpolarized noble gases (bottom) have a much larger percentage of atoms aligned with the field, which, even though the density of atoms is less, produces a larger signal.



we don't yet have the ability to produce a beam of polarized protons. So that's one problem with this field. U.S. scientists would like to build a somewhat lower-energy collider, but to really see the gluons, we need the highest energies possible.

A publication from a typical collider experiment today has about 500 authors' names on it—far more than even the publication from our SLAC experiment. It's amazing that you can still *see* the initials! And at an experiment at CERN, which is the next frontier in energy, the size of the collaboration would be approximately 1,000 names. This is just a fact of life in high-energy physics. So it was time to start looking for other things to do, especially with 10 years to wait, and that's how we got into the medical spin-off.

Before we did our SLAC experiment, it took lots of money and lots of work from a big team of atomic physicists to produce polarized ^3He . Before that, the most anyone had produced was about one cubic centimeter of it, so we had to figure out how to make the stuff by the liter. Some of the atomic physicists in our group, who weren't inclined to hang out very long in these large collaborations, realized very quickly that you can actually use this polarized gas for something else—magnetic resonance imaging (MRI, which also works on spin). First of all, a noble gas like helium (^3He is just like ^4He in this respect) is completely safe in the body. And the second

important thing is that the high polarization gives you control over a large number of spins, so that you can produce very large signals. By combining the technology of MRI with this technology of polarizing a harmless gas that can be inhaled, the lungs could be imaged.

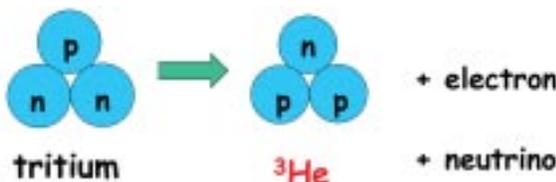
When you have an MRI scan, you put yourself inside a large, superconducting magnet with a very high magnetic field. The signal that makes the image comes from water inside the body. The spinning protons in the hydrogen nuclei act like tiny magnets and align their spins with or against the magnetic field. The higher the field, the greater the proportion of protons that line up with it, but the excess is very small even in a strong field—on the order of 10^{-4} (one in ten thousand)—and your signal strength is proportional to that number. The advantage of a water signal is that of density: you have lots of nuclei to look at, but you do have to go to extremely high magnetic fields to get a nice image, which is why we have to use these large MRI monsters.

But remember that we can make a noble gas with 50-percent polarization—a gain of four orders of magnitude. We lose density—there aren't so many nuclei to look at—but the polarization is so high that we can still get large signals. It's very hard to image the lungs with a conventional MRI scanner, because you get no signal at all from the air spaces, plus the water content of the lung tissue and the mucous membrane varies widely. But with this hyperpolarized ^3He , wherever the gas goes, you see a signal.

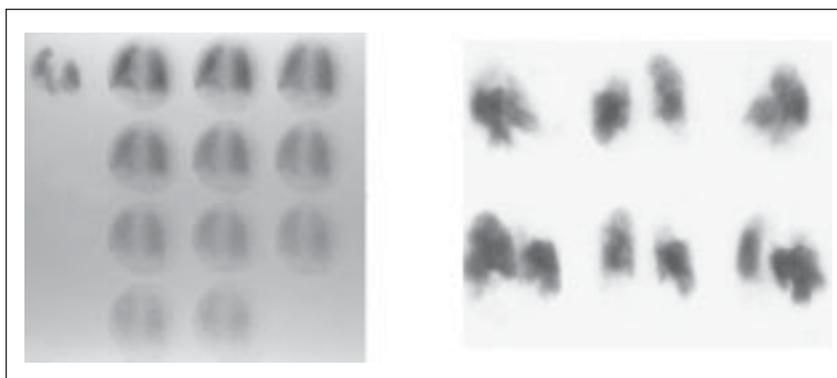
There is one little problem with ^3He : unlike ^4He , which is available everywhere, ^3He comes from weapons programs. So it's good to have access to a good weapons program if you want to do this type of research. I'm not going to get more political than that, but if you have lots of tritium, the price of ^3He goes down, and if you have a limited supply of tritium, which is used in nuclear bombs, it goes up. The price per bottle fluctuates from \$100 to \$300; it's supply and demand. Tritium, a radioactive isotope of hydrogen, consists of two neutrons and a proton. It decays into ^3He —two protons and a neutron—which is *not* radioactive but absolutely stable and safe.

Now, it turns out that there's another noble gas that is of no interest to high-energy physicists but is interesting for doing medical imaging, and that's xenon. The isotope ^{129}Xe has just the right number of protons and neutrons added up, (meaning an even number of protons—54—so that they will pair off and cancel out, and an odd number of neutrons—75—so that there will be one left over to polarize), and it also has a spin of one-half. It's not radioactive, and like helium, it's safe to inhale. Helium, as you know, is used for balloons, and kids inhale it all the time—the only effect is that your voice gets very high. Xenon is used in bright flashlamps, and if you inhale xenon, your voice

Tritium, a radioactive isotope of hydrogen used in nuclear bombs, consists of two neutrons and a proton, which decay into two protons and a neutron: ^3He , plus a couple of other little things.



A breathing rat lung (top), as well as a human lung (right) were imaged using ^3He . (Rat lung courtesy of G. Allan Johnson and human lung courtesy of James MacFall, both of the Duke Center for In Vivo Microscopy, an NIH/NCRR National Resource.) These images are clearly far better than the V/Q scan of a human lung (below) currently used by doctors. (CAT scans can produce nice lung images, but only with high doses of radiation.)



gets very low (which, you will remember from Physics 2 at Caltech, is because the speed of sound in gas is dependent on the mass of the gas nuclei). ^{129}Xe is much easier to obtain than ^3He ; it's cheap and plentiful, and you don't need a weapons program. Xenon exists in the air at 87 parts per billion. It's very easy to separate xenon out of the air—something that can be done for about \$10 a bottle. About 26 percent of xenon in air is ^{129}Xe , which is the spin one-half isotope that you need in order to see signals. The signal is diluted, because about three-quarters of the xenon is unpolarized. Although we can get much higher polarization for ^3He , it takes hours or days to achieve, as I mentioned earlier. You have to have high-powered lasers and be very patient. And, while our ability to polarize ^{129}Xe is limited (about 5 to 6 percent), it takes only tens of seconds to get to the maximum value. So there are two good possibilities for noble-gas imaging, each with different advantages and disadvantages.

When we compare the magnetization of the signal of water (from a conventional MRI scan) to the signal of polarized ^3He , we find that they're roughly similar. Magnetization is roughly the magnetic moment times the density times the polarization, and the magnetic moment of water and ^3He are similar. The density of water in the body is, of course, much higher than that of an inhaled lungful of ^3He , but the polarization of the ^3He is much larger than the polarization of water. Multiplying these things together gives a ^3He signal that's roughly 10 times bigger than the water signal, but because there are details I'm leaving out, in the end they are comparable in size.

At left is a human lung image using polarized ^3He gas, made in the mid '90s at Duke University. The radiology department at Duke worked with our Princeton collaborators from the SLAC experiment to produce the polarized ^3He gas. You can see that it already makes a very nice image of the lung, and there have been improvements since then. The group also has made dynamic images of the lung of a breathing rat.

Compare this to the image at left, which represents the current lung-imaging technology. If doctors are worried about a possible blood clot in your pulmonary vessels, they'll give you a V/Q scan, which is a measurement of the ventilation of the lung and the perfusion. The perfusion is especially important, because that's what will tell you where the clot is or whether there is indeed a clot there. A radioactive dye is injected into the body, which shows up the structure of the lung, as seen in the right-hand set of images. At the same time, the doctor checks the ventilation to see where gas is going in the lungs, which is the left-hand set of images. You can see that the ventilation pictures have much worse resolution than the Duke group's image. The ventilation images were made by inhaling ^{133}Xe , which actually *is* radioactive. It's an FDA-approved procedure, and these



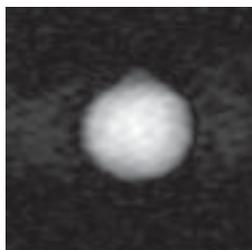
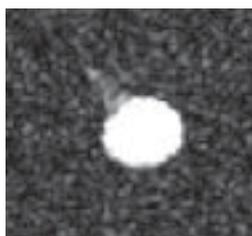
Left: The small (big enough for wrist or rat), low-field scanner in a Stanford electrical engineering building. Below it is a blown-glass cell of polarized xenon, and below that, the scanner's image of the cell. The Stanford scanner can also make images of a water cell (bottom).



scans are routine today, but I would much rather inhale spin-one-half, stable, nonradioactive ^{129}Xe than this stuff. So there should be no discussion about the safety of inhaling ^{129}Xe , and in the end you would also get a much better ventilation image.

Now I'll get to my own current research, which is a collaboration between Stanford and Caltech—"Stantech," we call it. (We decided that Caltech didn't sound as snazzy.) Stanford is very powerful in magnetic resonance imaging, plus they have a medical school and a hospital, which gives them certain advantages, so I gave in to putting their name first in Stantech. Caltech has the experts in polarizing a noble gas, and you need both in order to do this type of research. My Princeton collaborators left physics five years ago to join the Duke radiologists, and I began getting into this field only over the last couple of years, so I needed a new gimmick. And Stanford has one: an electrical engineering group (particularly interested in cardiac imaging) is trying to develop low-field MRI techniques to compete with high-field techniques—and which will have a price tag a hundred times less per scanner. So we linked ourselves to the low-field imaging program at Stanford. From the atomic-physics point of view, we don't care at all what the magnetic field is. Using our polarized noble-gas technique at a low field (30 gauss) is just as effective as doing it at high field as far as we're concerned. There may even be some advantages as well, compared to high field.

There's one minor problem: although the Stanford engineers collaborate with the medical school and all *their* scanners are located in the medical school, the low-field scanner that *we're* tied to is in the basement of an electrical engineering building that is not approved for animal imaging. So none of the images from our collaboration over the last year and a half are of animals. This is really unfortunate. We wrote a grant pro-



posal to the American Heart Association last year that got rave reviews. The Stanford cardiologists supported us, but we got turned down because we said we wanted to image a dead animal; we figured, a dead animal, a rat, who cares? But it turns out you can't do that. Dead animals turn out to be just as politically sensitive as live ones. ("How did you get the dead animal? Did you kill it?") They picked up on this because of the scanner's location in the nonapproved electrical engineering building. We will resubmit that proposal next year and drop the rat comment. We can develop the technology without rats.

Xenon has several potentially useful properties. It dissolves in the blood and even keeps its polarization there for a few seconds. And because xenon is a large atom with a large nucleus, it has large chemical shifts relative to its environment. (Without going into details, this means that the radio frequency at which a xenon atom shows up in the scanner is very sensitive to that atom's chemical environment.) For example, it has been shown that nuclear magnetic resonance scanning of xenon in oxygenated, as opposed to deoxygenated, blood will cause a shift in the signal that can be separated out.

Now comes the caveat: it turns out that xenon is an anesthetic. If you inhale a lot of xenon, it does interact with the body, which ^3He doesn't. This has never stopped doctors from putting radioactive ^{133}Xe into people's lungs, but it does place limits on the amount you can inhale. (You can actually inhale quite a bit before you pass out, but it's officially a drug.)

We spent enormous effort on getting polarized ^3He working at SLAC in our high-energy experiments, and we're just getting started on ^{129}Xe . So we're looking closely at the atomic physics of xenon. From the atomic-physics point of view, the big problem is that at high densities, xenon depolarizes rubidium. Typically, we can polarize xenon at only about the 5 percent level versus 50

The author finally sees his first name in a publication with only seven others. (Albert Macovski, a renowned medical-imaging engineer, also held a patent, now long expired, for color TV.)

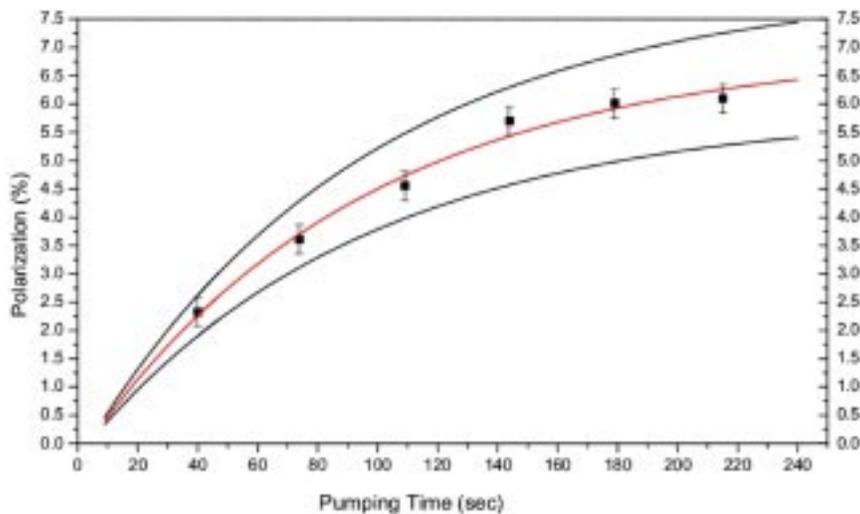
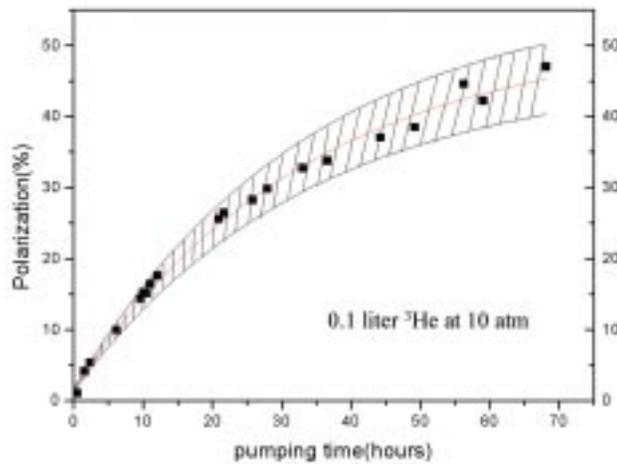
Low readout field magnetic resonance imaging of hyperpolarized xenon and water in a single system

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Using a low-field magnetic resonance scanner, we have obtained images of gaseous polarized ¹²⁹Xe and water cells at room temperature. This potentially low-cost imaging technique offers the possibility of high-resolution imaging using both polarized noble gas and proton magnetic resonance imaging of tissues in the same scanner. © 2002 American Institute of Physics.
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Recent work by Guodong Wang obtained a spin-up curve (top) for a liter of polarized ³He of close to 50 percent—but with a pumping time of 70 hours. In contrast, Wenjin Shao's spin-up curve for ¹²⁹Xe (bottom) gets to only 6 percent, but in four minutes.

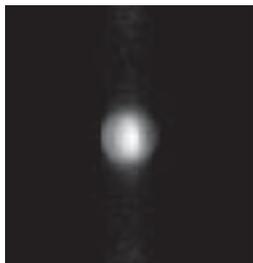
percent for ³He, so the ³He images are much better at the moment. My graduate students Wenjin Shao and Guodong Wang are trying to get the polarization of ¹²⁹Xe up to the 50 percent level, which will give us a 10-times-bigger signal.

We do the polarization studies at Caltech with the four big, fancy argon-ion Ti:sapphire lasers that I snagged from the SLAC experiment and brought home to my lab, but the simple imaging studies at Stanford require only a diode laser and a conventional magnet. We make a little cell of xenon, which we stick into the home-built Stanford low-field scanner. It has a small bore; you could image your wrist—or a rat. The center picture at the far left of the opposite page is an image of our xenon cell from the Stanford scanner. You can see that even with only 5 percent polarization, we get decent results.

Compare this to the nice resolution of the water image below it from the same low-field scanner. The Stanford group has focused for 10 years now on getting water images at low field that can compete with high-field ones. We are actually the only group in the world that can image both water and a hyperpolarized noble gas in a low-field scanner. (Harvard has a low-field project—even lower than ours—using a noble gas, but they can't get water images.)

The paper we published recently on the work has only eight authors—four from Stanford and four from Caltech. And my first name actually appears! For a high-energy nuclear physicist, that's really something to savor.

What are we planning for the future? We're continuing to work with both ³He and ¹²⁹Xe. While imaging with xenon at Stanford, at Caltech we've also gone back to producing polarized ³He cells to be used for imaging, as well as continuing to work on improving the xenon polarization. We're using our big laser system to study the detailed physics of xenon with other alkalis besides rubidium, such as cesium and potassium.



Stantech's first image of a ^3He cell from the low-field scanner, made by Tina Pavlin last May.

You need an alkali metal, which has one electron in the outer shell, to make the process work.

Xenon has another advantage: it freezes at liquid-nitrogen temperatures, which extends the lifetime of the polarization to hundreds of hours. A group at Princeton has already done this. We haven't done it yet, but what's nice about this property for medical uses is that, in principle, we could produce polarized xenon in a lab at Caltech, freeze it, keep it in a magnetic field, and ship it all over the country to different imaging centers. If we can develop the technology to get a high enough polarization, we could in principle become a little "factory," producing the stuff, freezing it, and shipping it off.

We're also studying the diffusion times of ^{129}Xe and ^3He , which are quite different. ^3He diffuses very quickly. Now that can be very good, because it will diffuse into the lungs quickly. But for imaging you'd like it to stay in place once it gets there.

We're also looking at an advanced technique

called spin-echo imaging, which is much quicker and could be important for functional imaging of the lung; and then, of course, we eventually hope to image animals and humans at Stanford. I expect that in the next year or two we'll be in that ball game.

Imaging techniques using polarized noble gases will be particularly handy for investigating asthma and cystic fibrosis (as well as chronic and obstructive pulmonary disease, emphysema, and lung transplant recipients), diseases in which it's important to look at how the lungs are functioning. It's not as likely to be helpful in lung cancer, although it's not out of the question that this type of imaging could see structural defects and nodules. We also think this sort of imaging will be especially applicable for children. You can actually get beautiful lung images with CT scans, but parents don't want to put their children in CT scanners because of the high radiation doses. MRI with a noble gas doesn't have any of the safety problems of CT scans.

In summary, research into polarized noble gases has broad applications, and until the high-energy physicists figure out how to produce polarized protons in an electron-proton collider, the fundamental physics research just has to wait. □

Emlyn Hughes, whose Seminar Day talk was adapted for this article (which lists his whole name as author), has been professor of physics at Caltech since 1999. He received his BS from Stanford in 1982 and his MA (1984), M.Phil. (1985), and PhD (1987), all in physics, from Columbia. In 1989, he returned to the West Coast to the Stanford Linear Accelerator Center, where he was a research associate from 1989 to 1992 and a Panofsky Fellow from 1992 to 1995. In that year he arrived at Caltech as an associate professor. Hughes was awarded a Sloan Fellowship and an ASCIT Teaching Award in 1997; in 1999 he won the Feynman Prize for Excellence in Teaching.

PICTURE CREDITS:
28, 30, 31, 32 – Emlyn Hughes; 30 – SLAC;
34 – Steve Conolly;
35 – Georgia Frueh;
37 – Lockheed Martin

The Caltech segment of "Stantech" includes, from left: grad students Wenjin Shao, who is working with xenon; Guodong Wang, who is focusing on ^3He ; and Tina Pavlin (fourth from left), who works with the imaging group at Stanford; Emlyn Hughes (behind Pavlin); and two technicians, glassblower Faye Witharm and lead technician Ray Fuzesy, a "technical wizard" who worked for 30 years at Lawrence Berkeley Laboratory in the lab of Owen Chamberlain, who won the Nobel Prize for discovering the antiproton.

