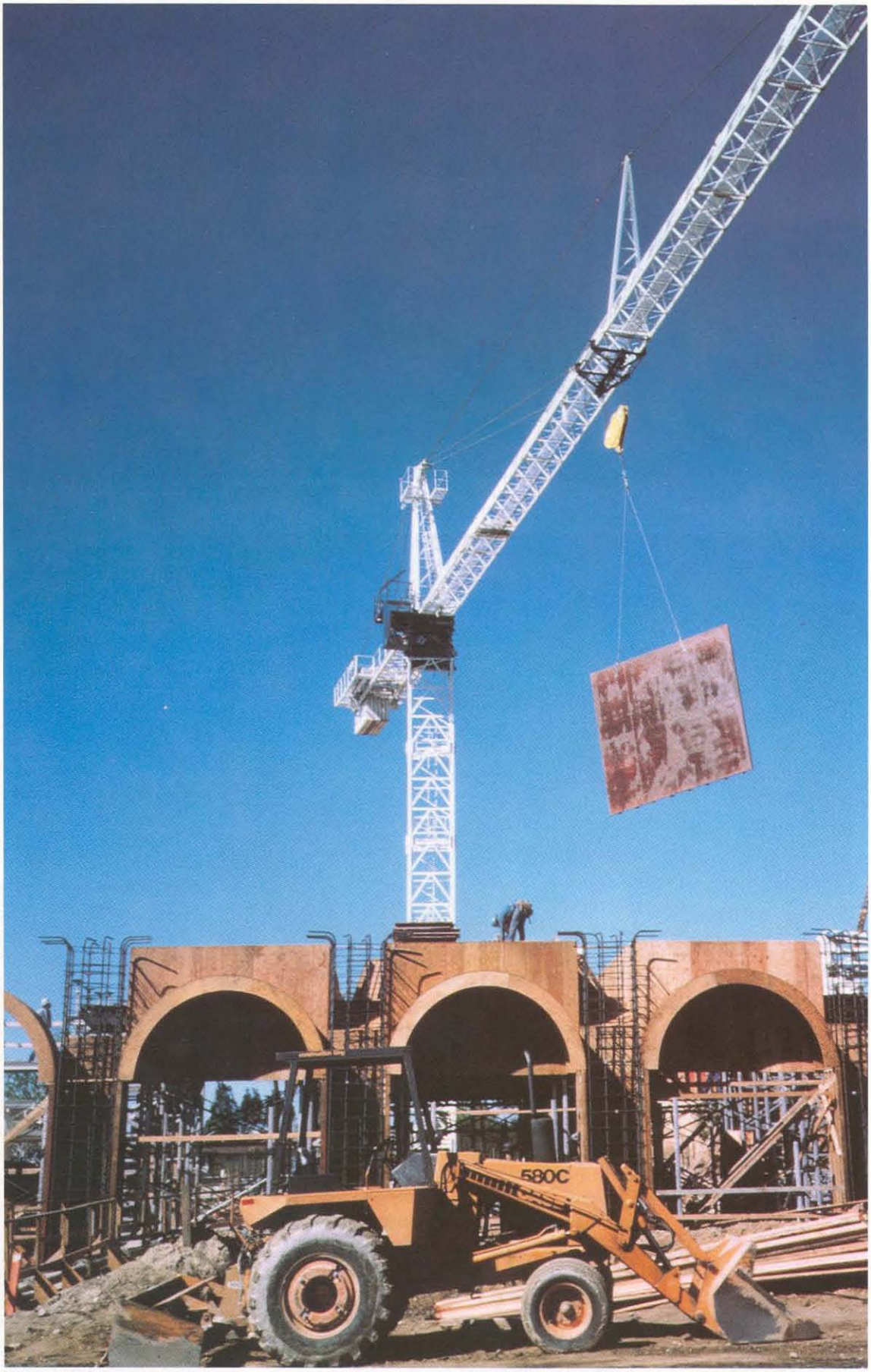
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Beckman Institute Becomes Concrete

The Institute will be supporting potential home-run hitters.

Once a gleam in the eye, then a hole in the ground, the Beckman Institute is rapidly rising in the northwest corner of campus. The official dedication is slated for October 1989, and the real dedication for several months later, when the interior is finished and the building is habitable. Even now, the prospective inhabitants are packing their bags, at least mentally, in preparation for the move-in.

Research in the Beckman Institute, in its standard press-release description, "will focus on the invention of methods, instrumentation, and materials that hold the promise of opening new avenues for fundamental research in chemistry, biology, and related sciences . . . an environment that will promote the initiation and early development of research that may be deemed too innovative for more conventional funding." In other words, the Institute will be supporting potential home-run hitters, whose research could cause far-reaching changes if it doesn't strike out.

Workers assemble the forms for the Beckman Institute's east facade. The arches open onto the central courtyard.

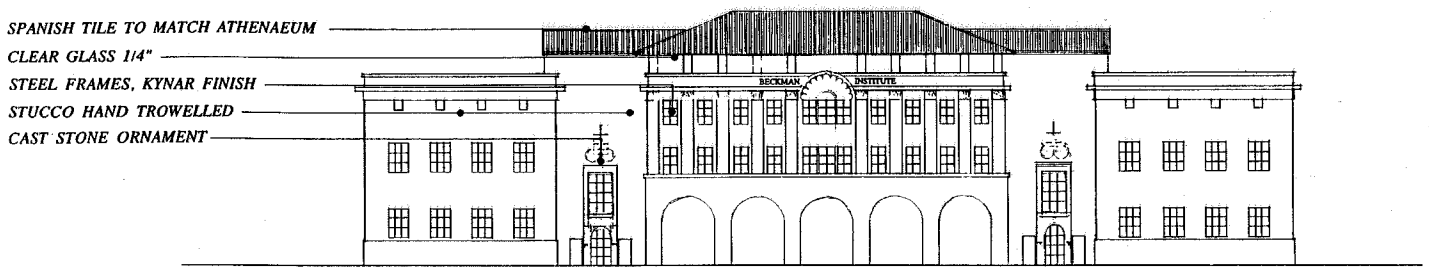
The Institute is the brainchild of Life Trustee and Chairman Emeritus Arnold O. Beckman, whose $50 million pledge sparked the project. The pledge includes an endowment fund that will provide seed money to get promising research off the ground. According to Harry Gray, the Beckman Professor of Chemistry and Director of the Beckman Institute, "This guaranteed base supports a project's most critical activities, and, by sharing the risk, will make it easier to attract outside funds."

The Institute will even have a farm team of sorts, a research grant program to fund small-scale preliminary work in the researcher's own lab. A grant will only last a year or two, just long enough to see how things go. When time's up, says Gray, "If it works, we'll stop funding it 'cause somebody else will. If it doesn't work, we'll stop funding it anyway!"

Research space at the Institute is divvied up into "resource centers" based on proposals the faculty submitted in early 1988. Each focuses on developing a particular area of technology. Part of each center's mission is to make the instruments or methods it develops available to the campus community, including undergraduates, in a walk-in, "user-friendly" facility. The Institute's starting lineup includes four centers, and a fifth may be approved soon. Final capacity will probably be seven or eight.

Three (two and two-thirds, actually) centers merge biology and chemistry. Bowles Professor of Biology Leroy Hood's Center for the Development of an Integrated Protein and Nucleic Acid Biotechnology will continue his group's automation of the analytic and synthetic techniques basic to molecular biology and genetics. Professor of Chemistry Jesse Beauchamp's Center for High-Performance Mass Spectrometry is working on a different approach to one of the same problems that would give biotechnologists a whole new set of tools. And two of the three principal investigators in the Structure and Spectroscopy Center (Gray and Professor of Chemical Physics and Biophysical Chemistry Sunney Chan) are looking at the chemical means to biological ends: how biomolecules move chemicals and energy.

The other occupants are doing straight chemistry. Shell Distinguished Professor and Professor



of Chemistry John Bercaw, the third collaborator in the Structure and Spectroscopy Center, is looking at catalytic processes. The Materials Resource Center will include Professor of Chemistry Robert Grubbs and Associate Professor of Chemistry Nathan Lewis, who will be exploring ways to make new solid-state materials with unusual properties, and Professor of Chemistry John Baldeschwieler, who will be setting up a scanning-tunneling and atomic-force microscopy facility to look at their creations.

"We'd rather seed something new that looks exciting than keep propping up something that isn't working."

The centers will vary in size and longevity. Beauchamp's will have four or five people; Hood's may eventually have as many as 30. In theory, everyone is a transient—doing a specific piece of work and moving on. According to Gray, "The larger centers, like Hood's center and the materials science center, will probably be there for a long time, but will emphasize different themes. People—perhaps even principal investigators—will come and go, but the fields are so broad that there is going to be something interesting to do for a long time. A smaller center, like Beauchamp's, is more narrowly focused on a certain problem, so either he will be successful and stay on, or be unsuccessful and quit."

Funding mechanisms will vary, too. Hood's center, for example, will live entirely on "soft money"—outside funds. "In fact," says Gray, "all successful centers will have a substantial amount of external support. The very high-risk centers will rely more on hard money to get started, but those that don't attract external funding after the first two or three years will certainly die. And we'd rather seed something new that looks exciting than keep propping up something that isn't working."

The resource centers will also attract outside collaborators, who might stay for six months or a year while they work on a particular problem. A Visiting Scholars' Center, complete with offices, conference rooms, and a lounge, will take up part of the third and fourth floors.

The building will also house some things not part of the Beckman Institute proper: additional space for computation and neural systems laboratories, various kinds of biology, materials science and applied physics, and the Caltech Archives.

While the above sounds simple, logical, and straightforward, it didn't come easily. The ideal Institute's mission had been defined very broadly, with the details to be penciled in later. But someone had to pick up that pencil before the real Institute could open for business. The first decision was to organize into resource centers. Others quickly followed: how would the centers operate? Who would occupy them? How much space and money would each one get, and where, exactly, would it go? All these questions fell to an executive committee to answer.

The committee's first project was drawing up a charter stating exactly what the Institute's mission was, and how to go about it. The Institute's novel approach to research meant that the usual rules didn't quite fit. But the new rules had to meet everyone's notion of how Caltech should operate. Jay Labinger, the Beckman Institute's administrator, helped Gray keep things on track, "basically making my life bearable," Gray says. It took a year and a half of

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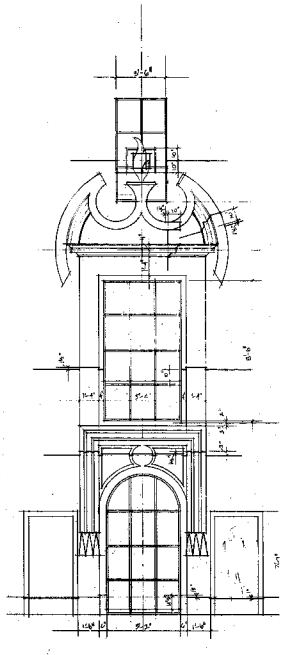


monthly meetings to hammer out a charter. Recalls Labinger, "The most difficult part was getting all the committee members in one room at the same time. You'd find out there's only one day when everyone's free, and it's not till the middle of next month. So we did a lot of work by memo. That charter went through I hate to think how many iterations. Harry and I would circulate a draft to the committee, and people would make all kinds of changes, and this kept going until everyone was happy. And then we took our revised semi-final version to the chemistry and biology divisions, who made changes, so we took it back and rewrote it again. Then it went to the administration, who had their own concerns, of course, and it finally converged into something everyone could agree on. But everything else really flows from that document."

What flowed from that document was step two: selecting the resource centers and allotting them space and money. These two tasks took about six months each. Says Labinger, "We had to cycle several times between the committee's reading of what each proposer really needed, as opposed to what they asked for, and what we could afford to give them. Space, for example: not only how much space, but where. Certain operations should really go in the subbasement, things that need to be shielded from vibrations. And some centers should be next to each other to foster interactions—Hood's and Beauchamp's, for example: their programs are quite different, but their goals are pretty much the same. And we didn't want to give away the whole building in the first round, locking ourselves in. But the leftover space had to be usable—not a closet here, a lab there, and an office somewhere else. And indeed, we have at least three good-sized contiguous areas left.

"And the budget is pretty much the same. The first few years are complicated, because you have heavy equipment purchases as well as salaries and operating expenses. Do we actually want to spend some of our capital on equipment? If we do, it's an investment in the Institute, but it takes dollars out of your endowment, so you have less income in later years. We have to decide all these things."

The committee will continue making these decisions over the years as resource centers come and go. Except for Gray, Labinger, and the biology and chemistry division chairmen, who serve *ex officio*, the members serve three-year terms expiring at staggered intervals, guaranteeing fresh viewpoints. This past fall, Giuseppe Attardi, the Steele Professor of Molecular Biology, replaced Professor of Biology John Abelson. The other members are: Hood; Grubbs; Bren Professor of Chemistry Peter Dervan; Chandler Professor of Cell Biology Eric Davidson; Chandler Professor of Chemical Biology, Emeritus, Norman Davidson, acting chairman of the Division of Biology; and Professor of Chemistry Fred Anson, chairman of the Division of Chemistry and Chemical Engineering. Members who do not have research going on in the Beckman Institute, such as Eric Davidson, bring valuable perspective to the committee, while the internal members, such as Hood, provide feedback on how decisions are working out in practice.

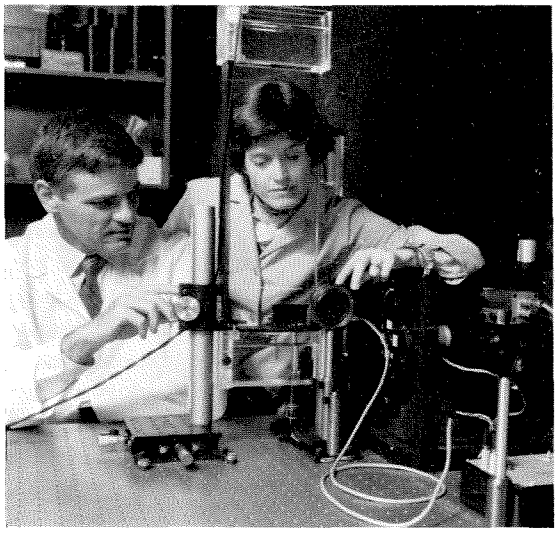
Lee Hood's Center for the Development of an Integrated Protein and Nucleic Acid Biotechnology will be the largest resource center by far, occupying the lion's share of the second floor. It's so large, in fact, that the National Science Foundation (NSF), which is providing most of the center's funds, requested that Hood step down as chairman of the Division of Biology in order to give it his full attention. It'll probably also be the longest-lived of the Institute's determinedly transient occupants. The NSF is funding the center as one of eleven Science and Technology Centers nationwide. (Caltech also has a half-share, along with Rice University, in the Center for Research on Parallel Computation, to be on Rice's campus in Houston, Texas.) The NSF has the option to continue funding successful centers for eleven years.

"The NSF grant relates to everything we'll be doing in the Beckman Institute, but it doesn't pay for everything," Hood explains. "Our work is divided into two components: one that develops new techniques and one that sets up a means to apply these techniques and make them available to the Caltech community, and, as outside companies get interested in producing the machines, to all scientists. The NSF grant essentially pays for the developmental component."

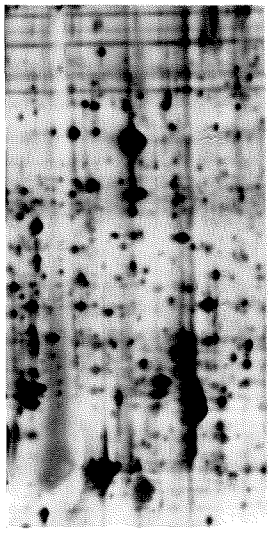
Once a rugged, "user-friendly" machine is produced, the applications team, led by Members of the Professional Staff Suzanna Horvath and David Teplow, work out the procedures the biological community will actually use.

The developmental effort falls into five subgroups. One, headed by Senior Research Fellow Michael Harrington, will be refining two-dimensional gel electrophoresis, a technique for separating complex mixtures of proteins. Another will improve ways to find the amino acid sequences of the minuscule amounts of protein 2-D gel electrophoresis isolates. New equipment to sequence and map genes is being developed by Senior Research Fellow Robert Kaiser's team. All of these projects need specialized instruments,

Right: Hood and Member of the Professional Staff Jane Sanders with the prototype DNA sequencing machine.
Below: Part of a typical 2-D electrophoresis gel (actual size). Standard gels are 20 × 16 centimeters.



A single microdroplet containing about 5,000 cells' worth of protein can yield several thousand spots.



which Charles Spence's group makes to order. And better computer systems to handle and store sequence data are being evaluated by Tim Hunkapiller, a graduate student, and scientists at Caltech's Jet Propulsion Laboratory (JPL).

Before you can even *begin* studying a protein, you have to isolate it—usually from a messy, complex mixture of other very similar molecules. To make matters worse, the most interesting proteins are often the rarest—perhaps one molecule in 100,000. One promising separation method, two-dimensional gel electrophoresis, sorts proteins in one direction by their net electric charge, then in another direction by their mass. An electric field applied to the "gel"—a sheet of polyacrylamide—makes the proteins move. A single microdroplet containing about 5,000 cells' worth of protein can yield several thousand spots on the gel, spots as small as 100 picograms (100 trillionths of a gram) of an individual protein. Although the method's extraordinary sensitivity has gained it wide acceptance since Patrick O'Farrell introduced it in 1975, it isn't used nearly as much as it could be. Reproducibility is a problem—even identical samples prepared by one person often come out a bit differently. The two separations use different gels, and a small alignment error during transfer—sandwiching the gels face-to-face and blotting the spots from one to the other—is almost unavoidable. Harrington's group is trying to develop a machine that will do the whole process in one step on a single gel. The other problem is that the technique *is* so good at separating components. Comparing gels from, say, cultures of normal and diseased cells should reveal missing or aberrant proteins as mismatched spots—a simple and powerful way to find the culprit. But the sheer number of spots, even if they stay put, makes it hard to say for sure that one spot appears (or doesn't appear) on both gels. So Harrington's group is collaborating with Jerry Solomon's image-enhancement and analysis team at JPL, "basically taking the algorithms developed for the Voyager missions and turning them from stars to molecules," as Hood puts it.

Once an interesting spot has been found, researchers need to be able to pluck it off the gel and determine part of its amino acid sequence. (The sample's usually so small that it gets used up before the complete sequence can be found.) Fortunately, a small portion of the sequence contains sufficient information to make a DNA probe that will seek out and bind to the protein's gene. Then the gene can be cloned—making millions of identical copies of itself—and its location on its parent chromosome, as well as its entire sequence, can be determined. Finding a protein's sequence is tiresome but straightforward: a well-known set of chemical reactions clips the first amino acid off of one end of the molecule (the so-called N-terminus), the freed amino acid is identified, and the process is repeated. But even small proteins are hundreds of amino acids long. It's grindingly slow manual labor, taking perhaps six hours per amino acid, but in 1967 a scientist named Edman designed some fancy electronically controlled plumbing that works automatically and much faster than a graduate student. Since then, Hood's group has

The central courtyard

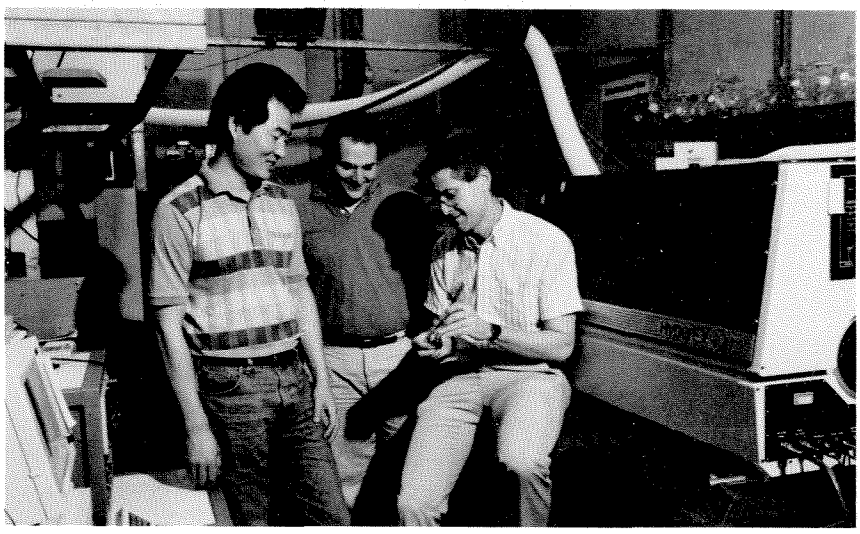
The most interesting proteins are often the rarest.

been refining the technology, making it faster and more sensitive. The latest equipment can sequence 10 picomoles of protein, and next year's model will be 100 to 1,000 times as sensitive. It will use fluorescent labels that, once attached to their respective amino acids, can be read off by a laser scanner similar to the bar code reader at a supermarket checkstand.

Kaiser's subgroup is working on a similar problem: analyzing the sequence of "letters" that make up the gene's coded instructions. They partially automated this chore in 1986, and are now working on a fully automatic design. The DNA to be analyzed is grafted into a bacteriophage, which churns out mass quantities of the stuff—a standard genetic engineering trick. But in this case, the bacteriophage lives in four flasks, one for each letter in the DNA alphabet. The nutrient soup in each flask contains all four letters (organic chemicals called nucleotides, actually), but a small proportion of one letter is defective—lacking a hydroxyl group needed to keep the chain growing. Instead, the letter carries a fluorescent dye, say, green for A, red for C, orange for G, and yellow for T. When a defective letter joins the growing DNA chain, growth stops. Since a defective G, for example, can wind up anywhere there's a G in the original DNA, at least one strand will end at each G. All four flasks, taken together, yield a set of strands ending with color-coded tags at every position in the original DNA sequence. Electrophoretically sorting the strands by length gives a laser-readable sequence of fluorescent bands whose colors match the letter sequence of the original DNA.

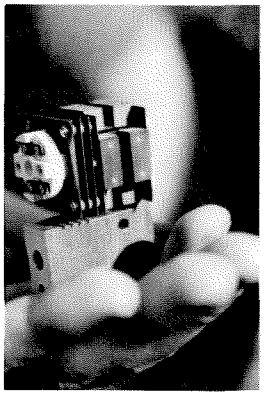
Sequence data from DNA or protein scanners can be computerized. Several sequence databases already exist, and the volume of information will grow exponentially as the sequencers become more powerful and in more general use. Sequencing the human genome (all the DNA in one set of human chromosomes—the biological equivalent of the Quest for the Holy Grail) would generate a string of data three billion items long. How does one store that much data accessibly? More important, how does one analyze it? The whole point of doing the work is to be able to look for similar sequences in different guises. Hunkapiller's team is looking at three approaches. In one, custom-built coprocessors or "superchips" could handle the computationally intensive parts of a pattern-recognition program. A program written directly in silicon, as it were, runs much faster than a similar program in a conventional computer that has to keep asking a memory chip what to do next. The other two approaches involve using parallel processors such as the Caltech/JPL Hypercube, which attacks massive problems by doling little bits out to interconnected small computers, or neural networks, whose unique design allows them to not only recognize patterns but discover them. JPL will collaborate on this project, and Hood hopes to pick the brains of the Computation and Neural Systems program too, which should be easy, since CNS will get space upstairs from him. The collaboration may even extend as far as Rice University, the other half of the Parallel Computation Research Center.

"This is a self-contained, modular attack on



Right: Graduate students Seung Koo Shin (left) and Dave Dearden with Beauchamp (holding sample cell) in the FT-ICR lab. The magnet is in the left rear; part of the laser setup is on the right. Below: The sample cell.

The entire assembly, sans magnets, is smaller than a pack of cigarettes.



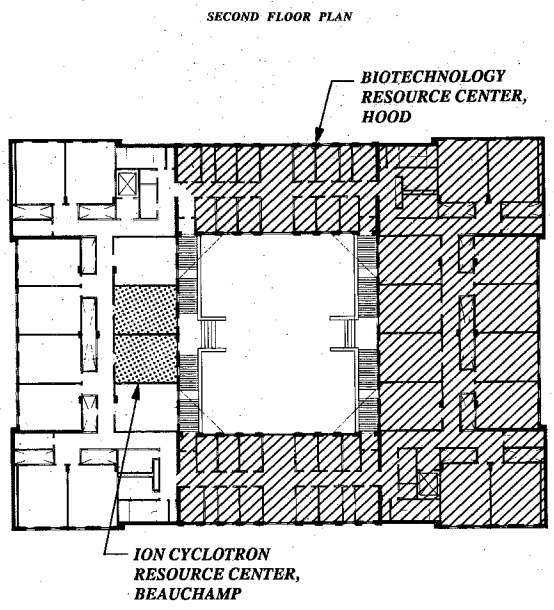
many of the fundamental problems of analyzing genes and proteins," says Hood. "It's already led to two applied facilities the Caltech community can use—one for synthesizing proteins and genes to order, which is four or five years old now, and more recently one to sequence proteins. In the not-too-distant future I hope to have a third one set up to sequence DNA at very fast rates. Then we'll be ready to undertake some really challenging projects, such as sequencing all human T-cell receptor genes." T-cell receptors are a critical part of the immune system. Their almost infinite variability, encoded in some 6 million letters of DNA, is crucial in the body's ability to recognize countless foreign and potentially dangerous substances. The most ambitious sequencing project to date, it would be a good dry run for various proposed attempts to sequence the human genome.

The smallest center, and the one with the most narrowly defined scope, is no less ambitious in its way. To be located just around the corner from Hood, Jack Beauchamp's group hopes to refine Fourier Transform Ion Cyclotron Resonance Spectroscopy (FT-ICR) to the point where it can detect a single ion. FT-ICR now detects as few as ten ions, a sensitivity Beauchamp will try to better by using superconducting magnets and by developing improved signal-processing techniques. Current equipment in Beauchamp's lab can handle molecular weights of up to about 1,000 atomic mass units (AMU). Beauchamp wants to reach 50,000 AMU, large enough to study small enzymes. The group will also try to improve an FT-ICR method for determining amino acid sequences in biological molecules. If they succeed, sequences could be run much faster and on much less material than is now possible.

FT-ICR identifies charged molecules by their mass-to-charge ratio. Charged particles, or ions, in a magnetic field travel in circles in a plane perpendicular to the field. At room temperature and typical field strengths (about 160,000 times stronger than the earth's magnetic field as felt in Pasadena), the circles are less than a millimeter in diameter. "Trapping electrodes" keep the ions from drifting along the field, and complete a three-dimensional electromagnetic "bottle." (The entire assembly, sans magnets, is smaller than a pack of cigarettes.) A trapped ion orbits at a characteristic frequency—its cyclotron frequency—proportional to the magnetic field strength and inversely proportional to the ion's mass. This frequency is generally in the radio frequency (RF) range. Applying an RF electric field at right angles to the magnetic field excites the ions, making them emit a signal picked up by electrodes at right angles to both fields. This signal contains a frequency corresponding to each ionic mass and is analyzed by a computer. The ions themselves stay in orbit indefinitely and can be redetected any time you please. Beauchamp notes, "About the only thing that can happen to the ion is it might react with a stray gas molecule, or it might diffuse to the wall of the sample cell and be neutralized."

Beauchamp's scheme to sequence proteins depends on getting them ionized, orbiting, and reacting with the right gas molecules. "We've had 20 years of experience with gas-phase reactions of ions," he says, "and we think we can design reactions that'll remove one amino acid at a

Gray's group has demonstrated that electrons can, in fact, leap across 20 atoms—a considerable distance—in less than one millionth of a second.



time." (Beauchamp's approach, incidentally, works on the so-called C-terminus, the opposite end of the protein from Edman's reactions.) With the endmost amino acid gone, an RF pulse would remeasure the mass, and the amount lost would fingerprint the missing amino acid. As the whirling ion continued to shed amino acids, its entire sequence could be read off.

This approach, if successful, would be about ten billion times more sensitive than current sequencing techniques, which require 10 to 100 picomoles of sample (roughly a quadrillion molecules). "But this comparison is misleading," says Beauchamp, "because those techniques work with the entire sample. We're only counting the molecules we can get airborne. Right now, that's fewer than one in a million."

Getting the molecules airborne is like lifting an elaborate sand castle—large and heavy, but very fragile. "You have to heat the sample incredibly fast—in nanoseconds (billionths of a second)—to vaporize the molecules before they're destroyed," Beauchamp observes. "If you heat the sample slowly, it'll fry itself." The group uses a pulsed, high-power laser to heat the sample. If Beauchamp can get the laser-vaporization process optimized, and put together a scheme of highly selective chemical reactions that will cleave one amino acid from the protein, he "can see this becoming a major focus in my group in ten years. We'll be able to study a tissue specimen by scanning a pinpoint laser over it and mapping molecules such as neurotransmitters. The collaboration with biology will be fascinating."

Three stories below, in the subbasement, Harry Gray will be using a laser spectroscopy lab to study electron transfer in proteins, a process fundamental to life. Whenever living cells store or use energy, electrons are transferred between molecules. Chemists used to think these transfers could only happen between two molecules in extremely close contact—rubbing up against each other, as it were. Gray's group has demonstrated that electrons can, in fact, leap across 20 atoms or more—a considerable distance—in less than one millionth of a second. These findings will affect such seemingly unrelated efforts as computer chip miniaturization, fuel cell development, and creating an artificial process that mimics photosynthesis, the method plants use to gather energy from sunlight.

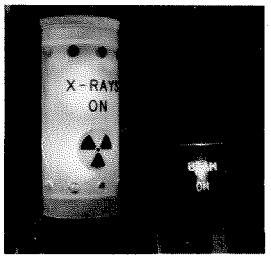
Gray's experiments use myoglobin, a protein related to the hemoglobin that carries oxygen in the blood. Myoglobin occurs in muscle cells, where it acts as a temporary oxygen storehouse. Buried within the myoglobin molecule is an iron atom, which acts as an electron launching pad. If a palladium or zinc atom is substituted for the iron, a pulse of laser light can launch the electron. The landing site is a ruthenium-ammonia complex that Gray's group attaches to the molecule's surface. The ruthenium can go in one of four spots where a histidine, one of the amino acids from which proteins are built, projects from the myoglobin's surface. Each site is a different distance from the iron, allowing transfer rates to be studied over a range of 13 to 22 angstroms. (An angstrom is one ten-billionth of a meter.) The amount of energy needed to make the reaction happen can be studied by modifying the takeoff and landing points—by substituting palladium for zinc at the launch, for example, or pyridine for ammonia at the splashdown.

Electron transfer also requires a very specific alignment of atoms along its path. Another series of experiments studies how altering that alignment affects the transfer rate. These experiments use altered forms of another protein, cytochrome c, where an amino acid at a particular point in the molecule is replaced with a different amino acid, a process called "site-specific mutagenesis." Since each amino acid has a different shape, changing one near the path alters the atomic alignments along the path. "We're trying to understand the rules governing these pathways," says Gray.

But there are many paths an electron could take through a protein's complex structure. In another approach to the same problem, Gray is building much simpler molecules with a single specific path designed into them. The path leads from an iridium atom, the electron source, to an electron acceptor. While an electron's flight time

through a protein is around a millionth of a second, flights through these smaller molecules take only a few trillionths of a second. "To measure events that fast," says Gray, "takes some pretty fancy lasers."

At the moment, Gray and Sunney Chan, the laser center's other user, must go elsewhere to look at their molecules. Both go to the Brookhaven National Laboratory in Upton, New York. Chan also goes to UCLA, New Mexico, and Michigan State. Chan remarks, "The events Harry looks at are a lot faster than mine, but we aren't really set up to do time-resolved spectroscopy of biological molecules in general. Having the laser center right here will give us a lot more flexibility in what we can do."

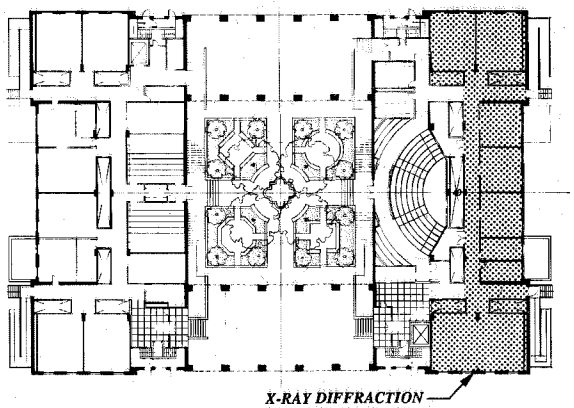


The catalysts work so quickly, like a conjuror palming cards, that you can't see what's going on.

Chan works with "biological machines." These molecules work against the tendency of things to spread themselves as evenly as possible, like a bagful of marbles spilled on a smooth floor. A chemical concentrated on one side of a permeable membrane, like a cell wall, will diffuse through it until the concentrations on both sides equalize—the state with the least potential energy. Chan's "machines" span the membrane, using the energy released as one chemical equilibrates to pump another in the opposite direction, against its concentration gradient. Cytochrome c oxidase, for example, is found in muscle cells, where it uses electrons going "downhill" to pump protons "uphill." Lactose permease, found in the membrane of *E. coli*, the microbiologist's pet bacterium, uses protons going downhill to accumulate lactose, a sugar used as fuel, inside the cell. Other machines pump wastes back out.

Chan uses lasers to watch his machines work. "These machines actually have moving parts," he explains, "and if we want to understand how the chemistry takes place, we have to watch the parts move." A loop of protein called an α-helix, for example, might partially uncoil and then coil up again as it pumps an ion along. Chan's group tracks these motions by stimulating the molecule with a pulse of laser light and recording the light the molecule emits in response.

"Very few people are working on these molecules because they are so big and complicated," says Chan. "There are probably only half a dozen groups in the world in this field, and our laboratory is probably the leader. The chemists haven't gotten around to synthesizing them yet, or trying to model their actions, because they are so big. But in ten years' time, chemists will be making them, so we're trying to learn the chemical principles they work on, the rules we need to remember when we want to design one of these machines." And the machines wouldn't have to be designed just for biological functions, either, but could be designed for industrial processes, fuel cells, and chemical sensors.

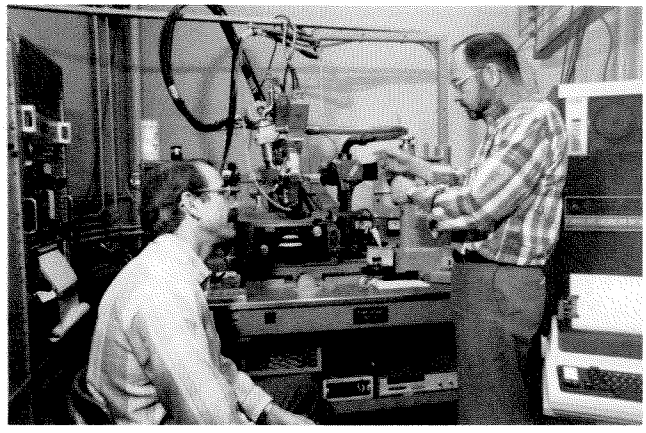


GROUND FLOOR PLAN

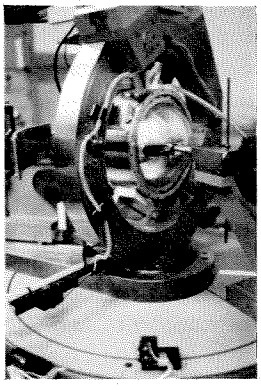
John Bercaw, on the other hand, will be using the x-ray crystallography facility—two stories up on the ground floor—to look at small molecules with molecular weights in the hundred-AMU range. Bercaw's molecules are organometallics—containing both a metal ion and carbon-based constituents. He is trying to work out the mechanisms behind some industrially important catalytic processes.

Take Ziegler-Natta olefin polymerization, for example—millions of tons of polyethylene and polypropylene are made this way every year. But no one knows exactly how the process works, not even Karl Ziegler and Giulio Natta, who shared the Nobel prize in 1963. The trouble is the catalysts work so quickly, like a conjuror palming cards, that you can't see what's going on. Says Bercaw, "We've made some molecules, scandium derivatives mostly, that are terrible catalysts because they work very slowly. But that allows us to study how the reaction mechanism works step by step. They're also very clean—they are selective, and they don't make side products."

Bercaw and his coworkers are also looking at the basics behind hydrocarbon oxidation—turning methane (CH_4) into methanol (CH_3OH), for example. It's the same approach: "We've made molecules that undergo very clean transformations that could be catalytic steps. I should point out that we haven't found a catalyst. Nobody really has found one that's practical, not like the Ziegler-Natta system. We're trying to do some basic science that might help us dis-



Right: Bercaw (seated) and Schaefer in the x-ray lab. The diffractometer behind them is one of three in the world that can cool a sample to 22 K, greatly reducing atomic motions that can blur crystal structures. Beckman Institute money will upgrade the computer system and other components.
Below: The sample chamber. The x-ray source is on the right, the detector on the left. The sample itself is no larger than a flyspeck.



cover a way to oxidize hydrocarbons very selectively." And if they can select a particular hydrogen atom from the dozens in a large hydrocarbon molecule, remove that atom, and replace it with an oxygen atom, presumably they'll be able to work backwards as well. "This could spin off to other processes. Hydrodesulfurization—removing sulfur—is practiced big time by the petroleum industry, desulfurizing crude oil."

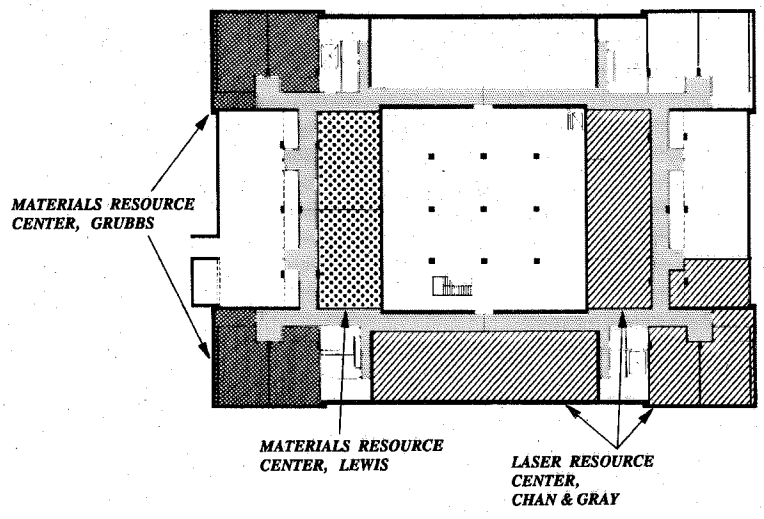
So they try whole families of molecules, an atom different here or there, like a shoe salesman proffering ten pairs of sandals to an indecisive customer. And when they find one that works right, "we dig in and really study it carefully. We investigate the catalyst's structure, and the product's and the starting material's, how they rearrange from one to the other, and how the reaction rates change as we make variations. Structure has a lot to do with function, and most of our structural information comes from x-ray crystallography. But the synthetic work, the kinetic studies, and the other analytical work will all be done elsewhere."

(The x-ray crystallography facility, incidentally, will be moved lock, stock, and Cu K α sources from the Noyes Lab subbasement. Senior Research Associate William Schaefer, its director, is ecstatic. "I get an office with a window for the first time since 1968!")

Bob Grubbs and Nate Lewis's facility, the Molecular Materials Resource Center, will share the Institute's subbasement with the laser labs. Grubbs is an organic chemist with a flair for making polymers (*E&S*, summer 1988). Lewis is an inorganic chemist who traffics in semiconductors. Together, they will beget hybrid organic/inorganic materials, while working separately on novel materials in their own fields of expertise. Their combined group may eventually include 20 people. "We're basically building properties into new materials from the molecular level up," says Grubbs, "rather than starting with the bulk material and working down."

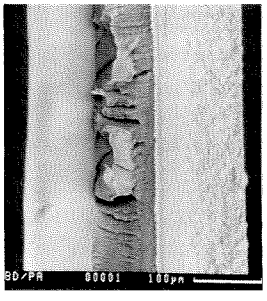
Grubbs can make polymers that can conduct electricity even though they don't contain any metal atoms. (A polymer is a very large molecule made up of hundreds of small molecules called monomers.) The method uses liquid ingredients, so the polymer can be cast into any shape or poured onto any unreactive surface. Conductivity depends on composition, which is easy to control with Grubbs's techniques. Grubbs and Lewis have already made organic diodes and capacitors from alternating films of polybutadiene, an insulator, and polyacetylene doped with iodine, a conductor. The two groups will collaborate in applying polymer films to semiconductor devices and exploring the novel types of switching functions, sensing applications, and other electronic uses that these new materials might make feasible.

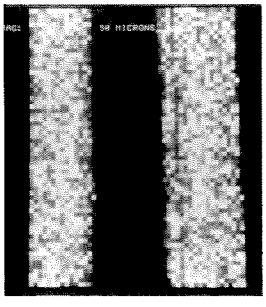
"To put this in perspective," Lewis explains, "to make a Schottky barrier, for example, which is a conductor-semiconductor junction used in integrated circuits, you take a metal—gold or platinum or copper—and deposit it on top of the silicon or gallium arsenide semiconductor. You can do this by evaporation—you just boil the metal—or by bombarding the silicon with a beam of metal ions." It's a brute-force, but effective, way to make electrical contact. Different metals have various "work functions," and the



SUB-BASEMENT FLOOR PLAN

'What happens when you mix cerium and uranium in a superlattice?'



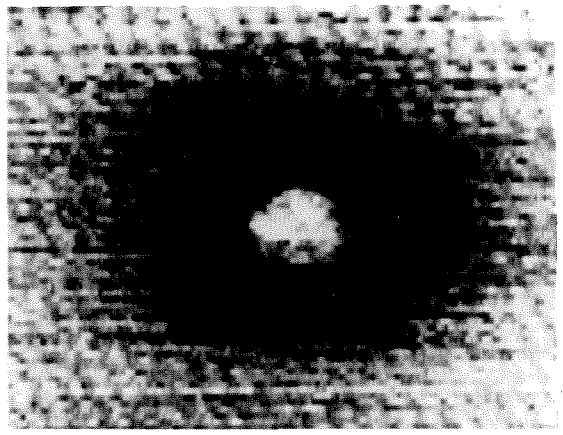


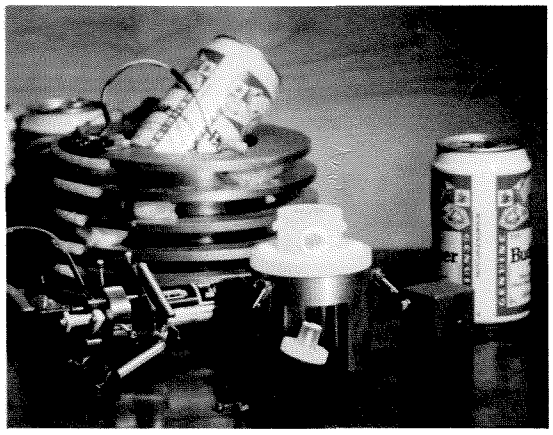
junction's properties should vary predictably with the metal. But things often don't work so nicely, presumably because the less-than-elegant assembly method mucks up the interface. "The metal may be diffusing into the semiconductor, or alloying with it, because the metal's very hot. But now Bob Grubbs comes along with a process capable of making a series of polymers with different work functions, and these polymers can be gently coated onto my pieces of silicon at room temperature. So people in my group started to wonder how these devices would behave, how the charge would move from one layer to the other, and what would happen at the boundary between an organic and an inorganic conductor. This project naturally brings together the organic chemist and the inorganic chemist, who normally wouldn't be talking together about this type of work. And that's what's unique about the Beckman Institute."

Grubbs can sprinkle different monomers through his polymers at will. The final molecule may have any number of regions of any desired size and composition. In principle, it's possible to make an insulating polymer with conducting regions small enough to behave as "quantum dots"—regions so small (20 to 100 angstroms across) that the electrons inside them can only move in specific ways. It might also be possible to make organic "superlattices"—ultra-thin-layer composites of two materials where each layer is only a few atoms thick. Although the superlattice's bulk composition is 50 percent A and 50 percent B, its properties aren't six of one and half a dozen of the other. Instead, the superlattice has "emergent properties"—entirely new behaviors derived from electronic states of the composite that are not merely the sum of the components' electronic states. (Grubbs' polymers aren't limited to electronic applications. Other projects have included creating a fluid that might be injected into the lenses of cataract patients' eyes as an alternative to hard plastic implants.)

On the other side of the street, Lewis is also interested in making exotic new inorganic materials. The semiconductor industry has spawned a sophisticated technology for making solids to order, techniques like molecular-beam epitaxy and metal-organic vapor epitaxy. But the machinery's expensive, and monopolized by the semiconductor industry, Lewis says, so, "If your garden-variety chemist says, 'Gee, what happens when you mix cerium and uranium in a superlattice?' no one's going to let him borrow their machine, which is dedicated to growing compounds the electronics industry needs, to find out. Yet these machines could make odd combinations of elements that are dissimilar enough to do really interesting things nobody's seen or predicted. So we want to put some of these machines in Beckman, where anyone can come in with an idea for a new material and make it, without having to build an instrument from the ground up. It will be a resource for the Caltech community. I'd also like to study how these machines actually make materials, the processes involved, and see if they could be improved."

The Molecular Materials Resource Center will also offer a facility for scanning-tunneling and atomic-force microscopy, which Balde-



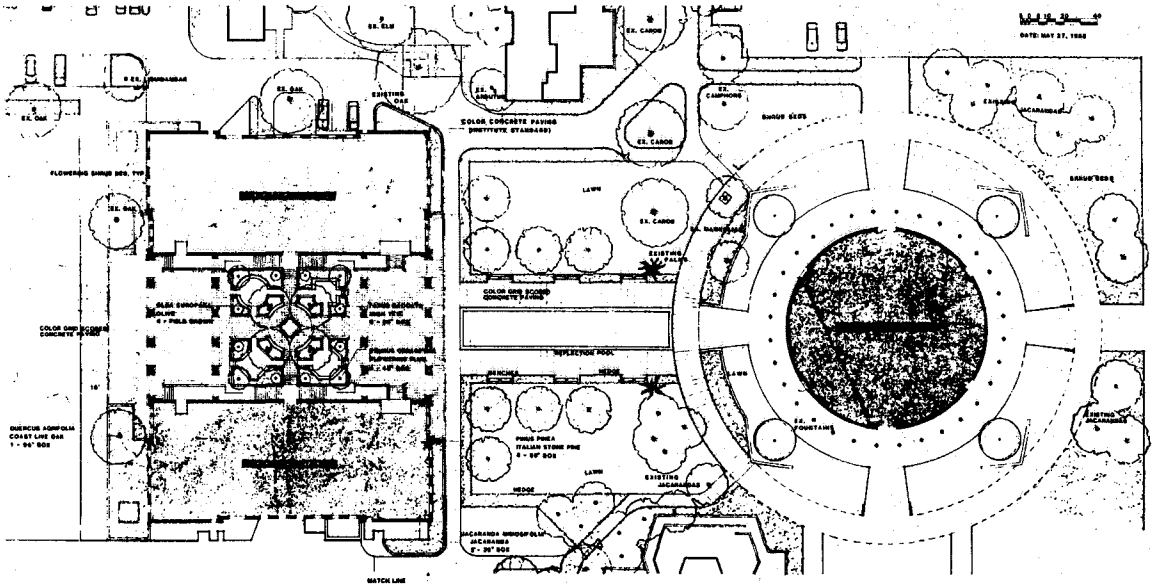


Far right: Not a can crusher, but the heart of a scanning tunneling microscope (STM). Right: STM image of a "blot" on the surface of a layered molybdenum disulfide semiconductor. The blot is roughly 10 angstroms in diameter, easily readable by STM. Opposite: Cross-sectional electron micrograph (above) and energy-dispersive spectrogram (below) of a nonmetallic capacitor—polybutadiene sandwiched in polyacetylene. Each layer is about 100 microns thick. The spectrogram shows iodine dopant as white spots.

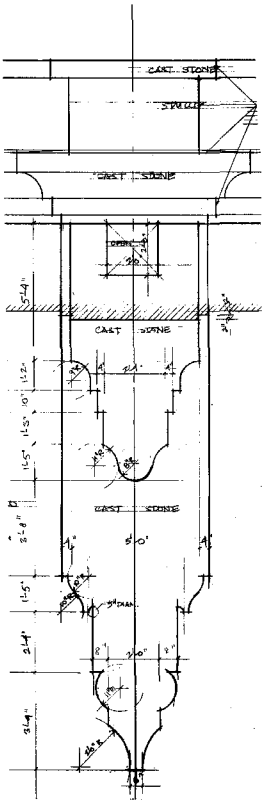
schwieler will administer. Both techniques measure atomic-scale forces between a solid surface (or even a single molecule) and a scanning, atom-sized probe, creating a three-dimensional picture of the solid so detailed that you can see individual atoms on the surface. The atomic-scale resolution makes these techniques ideal for looking at the resource center's new materials, which have been engineered from the atomic level on up, and other researchers on campus are eager to apply this technology to their own work. Baldeschwieler hopes to expand the biological applications in particular. It should be possible to look at a single protein molecule in a water solution, for example, and see the convoluted, three-dimensionally folded shape the protein assumes to do its job—a dainty shape that's distorted or lost when the protein is concentrated, purified, freeze-dried, crystallized, or otherwise manhandled by the techniques normally used to determine molecular structures. And there's the possibility of making ultracompact data systems. The probe could be used to create a tiny blot—only a few atoms in diameter—on a clean, smooth semiconductor surface. The same probe, scanning the crystal later, could read the blot as a digit of binary code—a blot is "1," and no blot is "0." "If we can figure out a way to make and read these blots reproducibly, we could increase the storage density on a memory chip by a factor of a million," says Baldeschwieler. "And we think we know how to make them."

But before anybody makes anything in the Beckman Institute, the building has to be built, preferably to a plan that meets the evanescent occupants' changing needs. "Dave Morrisroe (vice president for business and finance and treasurer) went to great lengths to be sure we got outstanding architects and contractors for this project," says Gray. Schaefer, the x-ray crystallographer, is the liaison between the architect, the contractors, and the Caltech community. Gray calls him the Beckman Institute's "acting director" in acknowledgment of his day-to-day responsibilities. Schaefer is certainly experienced—he helped convert Mead Laboratory into a showplace teaching lab, and has supervised the rehabilitation of other chemistry buildings. "So when the plans for this building became a reality," Schaefer says, "Harry asked me to help out. It takes an awful lot of time, but it's fun. It's my contribution." Schaefer spends his time worrying about details so the principal investigators don't have to. Details of the lab setup—what utilities are provided and where—and details of the decor—the color of the seats in the auditorium and the tiles in the courtyard. Even whether the U in "BECKMAN INSTITUTE" is rendered as a U or a V. "The architect's designer, Tim Vreeland, is specifically trying for the look of the old campus," says Schaefer, "the South Houses, and the Athenaeum. But it's not clear that it should be a V just because of that, and most of us are modern enough to think a V looks kind of silly. What do *you* think?"

Although the building will recall the old campus, changing times and economics means there will be no elaborate embellishments like the stonework crabs and sunflowers on Kerckhoff, or the Tree of Life on North Mudd.



Landscape plan: Beckman Institute on the left; Beckman Auditorium on the right.



"Vreeland put in some nice details, though," says Schaefer. "Like the big reflecting pool between the building and the Beckman Auditorium. He showed us a design for the decorative tile at the bottom of the pool, and it immediately recalled the double helix of DNA. And there'll be an abstract sculpture in the courtyard. Harry suggested that since the building relates to biology and both organic and inorganic chemistry, how about using a model of ferritin, an iron-containing protein? Its structure had recently been determined, but the only thing he could remember was that it had 4-3-2 symmetry. So I designed this geometric solid with the same 4-3-2 symmetry, and the 24 points on the solid represent the 24 subunits on the ferritin molecule. Of course, it doesn't look anything like the protein itself. We've thought about a plaque explaining it, but it seems to me that if you don't put a plaque up, it would be an awfully good question to ask during freshman initiations."

The main architect, A. C. Martin, and the lab designers, McClellan & Copenhagen, have both worked with Caltech before. They began by interviewing everyone who was known to be moving into the building, resulting in a bound volume two inches thick from which McClellan & Copenhagen derived their lab designs. These detailed layouts, with fume hoods and workstations, chilled water lines and compressed air outlets, and major pieces of lab equipment all drawn to scale, go to A. C. Martin for translation into working drawings. Says Schaefer, "I have to check all these things, make notes on them, and go back and forth when they don't match. Then there's a four-hour meeting once a week with both sets of architects, the Turner Construction people, and Physical Plant to discuss what's going on. Physical Plant has a lot of responsibilities, too—there are all kinds of permits you have to get, plans and documents that have to be filed with all these different agencies, logistics to think about—Bob Fort (director, Physical Plant) and Mike McCallan (manager, Engineering and Estimating) have gone way out of their way to make sure this project gets done right and on schedule. (Gray agrees, "Bob and Mike deserve a special vote of thanks.")

"You have to think of everything. The doorway sizes were based on the lab equipment. We worried about hallway width. Corners. Down in the subbasement, in the laser lab, they wanted these Newport optical benches—six- by twelve-foot tables two feet thick. How do you get them down there? The architects added an areaway alongside the building, so you could drop them down the areaway. Then Tom McClellan made a small model to be sure you could get them around the corner once you got them in the hallway. The laser lab doors are double doors, like in the Noyes Laboratory of Chemical Physics. A lot of what's going on here comes from our experience with Noyes. Noyes was designed by the late Holmes Sturdivant, a professor here for many years. He was a master of detail who spent enormous amounts of time worrying about these things. We've benefited a lot from him."

As we all will from the Beckman Institute.□—*DS*