Chemical Synthesis
A New Lab Gets It Together

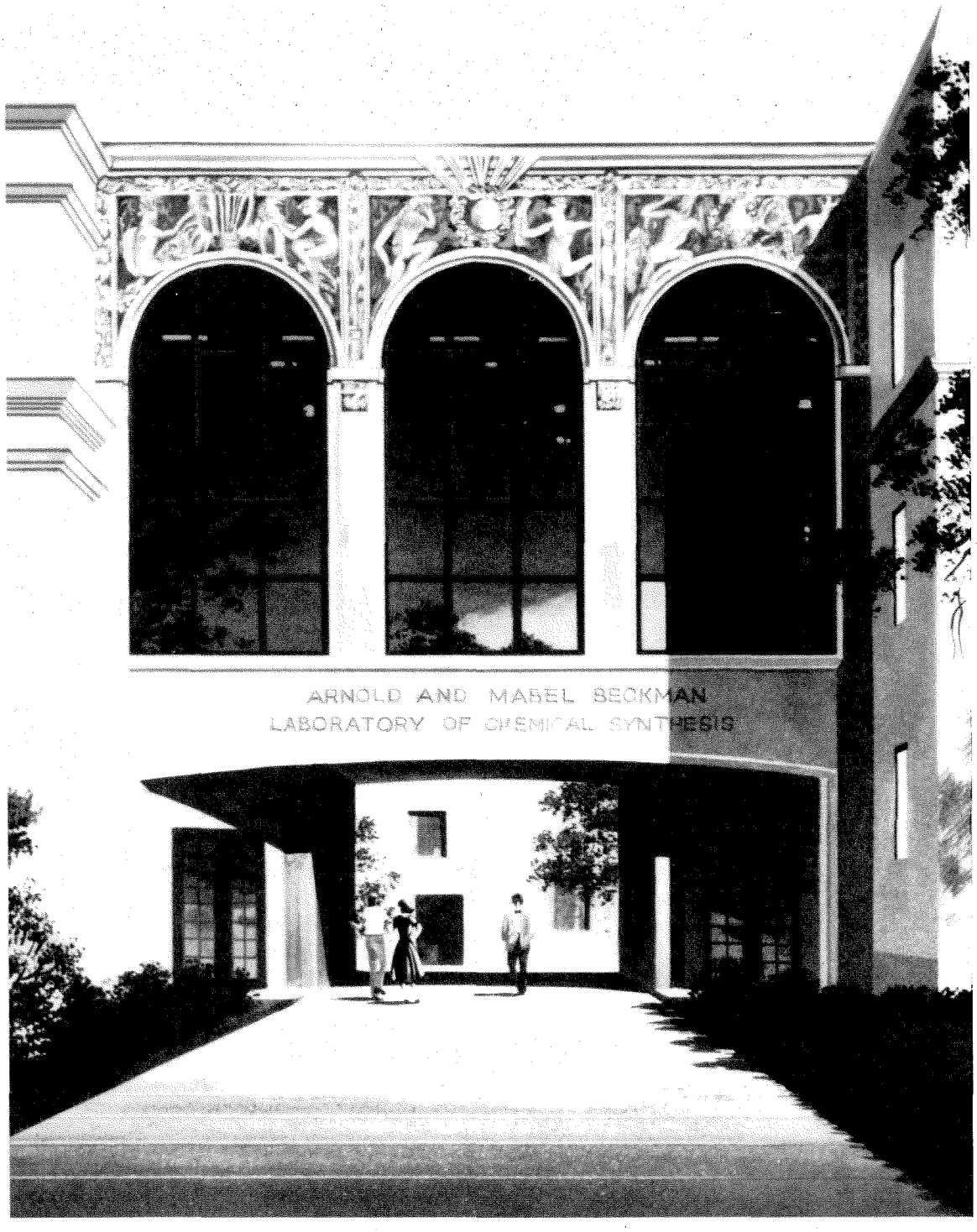
Because synthetic chemists are basically molecule builders — all kinds of molecules — they cross the classical boundary between organic and inorganic chemistry. By emphasizing this commonality, the new Arnold and Mabel Beckman Laboratory of Chemical Synthesis at Caltech makes a significant departure from tradition, reorganizing (one could even say synthesizing) chemistry in a region where organic and inorganic belong together.

The new laboratory, fully stocked with state-of-the-art equipment in six customized labs, also reflects a revolution in the way research in synthetic chemistry is done: in the past few decades it has become instrumentation-intensive. The tremendous growth in analytical instrumentation has expanded productivity and precision by orders of magnitude, making it possible now to design and build complex polyatomic molecules to atomic specifications. Specific properties can be designed into the molecules — properties with the potential for extraordinary applications in medicine, industry, and research. With the instrumentation available today, the Caltech research groups are developing such novel products as new catalysts to convert simple chemicals into more complex and valuable compounds, new enzymes engineered to possess useful properties not found in nature, and new molecules to transport drugs in the body. "Synthetic chemistry has reached a new level of sophistication," says Peter Dervan, professor of chemistry and chairman of the new laboratory's steering committee. "A lot of new science is emerging."

Beckman Instruments, Inc., the firm that Arnold Beckman founded 50 years ago, has been an integral part of this revolution in chemistry and chemical biology. So it's particularly felicitous that a $6.5 million gift from Arnold and Mabel Beckman made the new Caltech laboratory possible. The firm has played an important role in the history of world science, creating the equipment that science required. Although Beckman maintains that luck played a part in his company's rapid growth, the phenomenal success of the company wasn't just good fortune, according to Dervan. "As a scientist, Beckman understood where science was going, and as a businessman, he set out to fulfill the need that he foresaw."

Before Beckman was a businessman, he taught chemistry at Caltech — and applied his inventiveness to a number of other tasks as well. He worked with the architect and contractor who built Crellin Laboratory of Chemistry and personally helped design the laboratory furnishings. He also provided crucial chemical evidence in a horse-doping case that resulted in the donation of the Norman W. Church Laboratory for Chemical Biology. It's historically appropriate, then, that Crellin (1937) and Church (1955) have now been reincarnated as the Arnold and Mabel Beckman Laboratory of Chemical Synthesis.

The idea began several years ago when

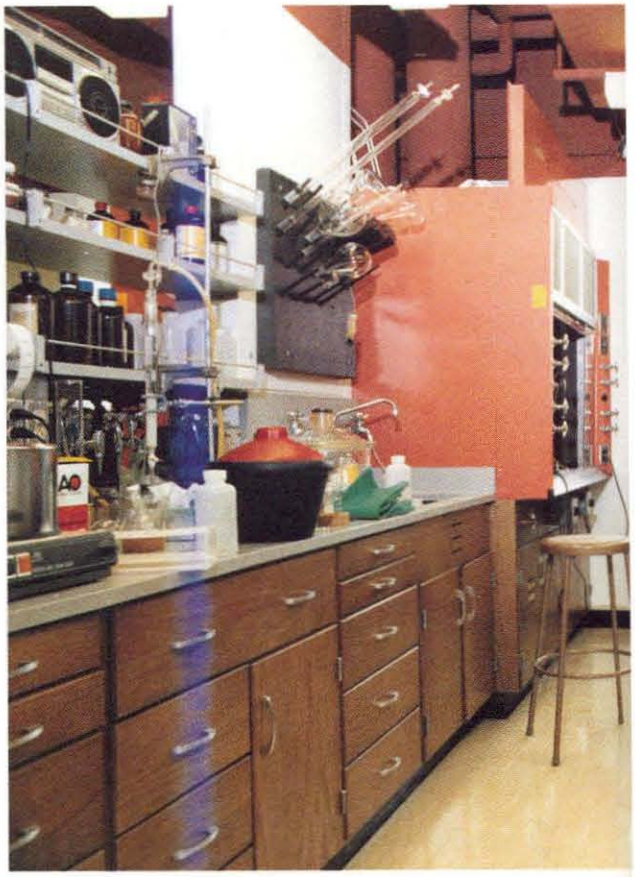


Harry Gray, the Arnold O. Beckman Professor of Chemistry, was chairman of the Division of Chemistry and Chemical Engineering. The synthetic organic chemists, housed in the half-century-old Crellin Laboratory, felt their facilities were inadequate to keep pace with the modern advances in instrumentation. They needed more instrument rooms, state-of-the-art analytical facilities, computers, and better safety features. And they needed such equipment as high-performance liquid chromatographs, DNA synthesizers, and high-field NMR spectrometers, as well as computer graphics to keep track of the hundreds of atoms in modeled molecules and to visualize and manipulate these models. Although the synthetic inorganic chemists had modern labs in Noyes Laboratory of Chemical Physics (the area into which they fell by tradition), they too were feeling the pinch. They also needed an array of equipment (such as x-ray structure-analysis and electrochemical instrumentation) — equipment that was very expensive.

Even though they worked in separate buildings, the organic and inorganic chemists were already loosely allied in a chemical synthesis group. The alliance had been fostered by the rise of organo-metallic chemistry, in which the molecules that the researchers work

with are hybrids — part organic and part inorganic. The borderline between organic and inorganic disappears in this case. Professors Robert Grubbs (organic) and John Bercaw (inorganic) were both doing the same sort of work in organo-metallic chemistry, work that Grubbs claims has caused him "identity problems" ever since he strayed across the artificial line into inorganic chemistry. The existence of "these two major groups that you can't put a label on," says Gray, facilitated the communication between the organic and inorganic chemists that led ultimately to their unification. "We've evolved to the point where we consider ourselves one community," says Gray. The new lab "recognizes and makes formal what we've been doing for some time. We're highlighting it now. We're going to drop the labels and admit that we're all making new molecules."

The old dividing line between organic and inorganic was largely a "turf" problem, according to Gray. Whereas in the past chemists were divided up into physical, organic, inorganic, and analytical, now some chemists think a more rational division would be into synthesis (making molecules), chemical physics (measuring properties and structures), and theory (applying computational techniques to structure and reactivity). Caltech's effort to diminish the artificial boundaries may lead the way to a new definition of chemistry subgroups. According to Dervan, "Already we're being sought out by synthetic chemists at other universities who want to see what we've done." Caltech is probably the ideal place to change definitions. "We're small enough,"



Center: Peter Dervan checks experimental setup in new six-foot hood.

says Grubbs, "and have students good enough that they can do this sort of thing — cross over and not get hung up on defining what they are. Our group is defined by how we think about chemistry, how we approach problems, and also by common instrumentation."

As the molecules that synthetic chemists build have grown more complex, the sophisticated equipment they need has become more expensive, a fact that made cooperation almost essential. Why not share? This also goes against the tradition that research labs have their own equipment, but the chemical synthesis group is quite satisfied with the concept. "By getting together, pooling everything, we hope to do better science," says Gray.

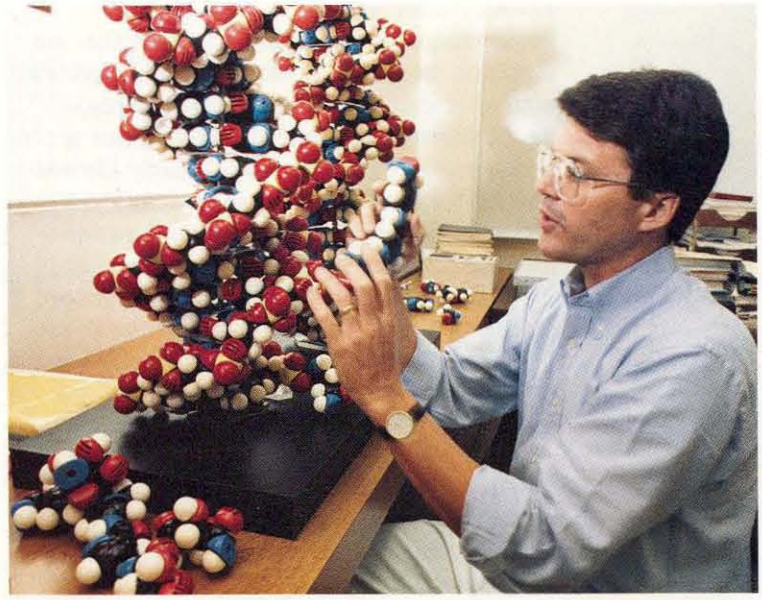
As the organic group's renovation plans began to take shape and they realized what they would need, not just to make their facilities adequate, but to play a leading role in chemical synthesis, the need for cooperation became clear. What also became clear was the need for more money than could be obtained from division funds and from grants. Arnold Beckman became interested in the project; he came out to visit with the chemical synthesis researchers and warmed to

Graduate student Eric Anslyn works with highly reactive compounds in a dry box.

the idea. From that point on he was intimately involved with planning the new laboratory. "A lot of the design — the way it's put together — came from sitting down and discussing it with Arnold Beckman," according to Gray.

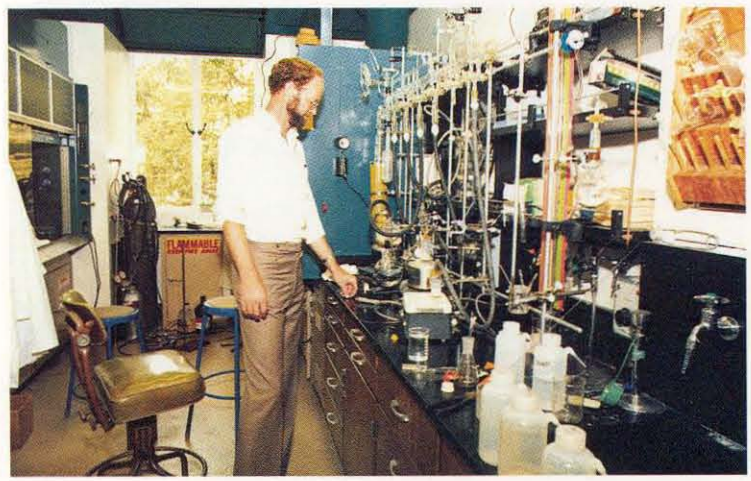
Of the Beckman gift, $460,000 per year over five years (a total of $2.3 million) is going toward instrumentation. Caltech will match this with an equal amount from grants and equipment funds. The rest of the gift was used to renovate Crellin and Church into the east and west wings of the new Beckman Laboratory — a total of 46,000 square feet, providing new labs for the organic synthesis faculty and students. The first phase of the lab, the top two floors of the west wing, is already complete; the three floors of the east wing will be finished in July; the last phase will be renovation of the west wing's first floor for a new senior faculty appointment yet to be made.

The buildings were gutted and the new labs designed from scratch. Preserving the exterior architectural detail posed some problems that wouldn't occur in new laboratory buildings. The hood ducts, for example, are usually built into double walls in new labs, leaving them windowless. Church and Crellin's windows were saved by constructing the walls for the ductwork between the openings.



Dervan builds a model of designed, synthetic, sequence-specific, DNA-binding molecules with double-helical DNA.

Each of the six research groups has 16 spaces for undergraduate and graduate students and postdocs. Each research group has its own instrument room and computer room (something organic labs never had before, says Grubbs), but beyond this basic framework, every lab is different. Each of the faculty members (Dervan, Grubbs, Dennis Dougherty, associate professor of chemistry, and John D. Roberts, Institute Professor of Chemistry) has customized his own. "It's a tremendous opportunity," says Dervan, "to tailor the labs for what you're doing." Dervan, for example, who shares the top floor of what used to be Church with Roberts, has pioneered methods for understanding how small molecules bind and recognize a specific sequence of DNA. His group needs such special equipment as high-speed centrifuges and



Bob Grubbs inspects one of the vacuum lines in his new lab.

DNA synthesizers, as well as the high-performance liquid chromatographs that are common to the other laboratories. Roberts's area of research is nuclear magnetic resonance spectroscopy and its applications to problems in organic and bio-organic chemistry (*E&S* January 1986), which requires a different laboratory setup and such equipment as high-field NMR spectrometers.

The second floor houses three research groups that span the two wings of the facility. In Grubbs's lab each of the 16 stations has its own vacuum line. Besides dry boxes and infrared and ultraviolet spectrometers, Grubbs also has a setup he has dubbed his "molecular weight room," for determining the properties of the polymers he builds, which have molecular weights of up to 50,000-100,000. He shares the second floor of Church with Andrew Myers, an assistant professor just hired from Harvard, whose research will be directed toward the synthesis of complex molecules of biological importance. Myers's quarters cross the bridge (with the Calder arches on the facade) between the two wings and tie the two sections together; his instrument room is behind the lower level of the arches. (The third floor, directly behind the sculptures, will house a computer graphics lab.) Dougherty and his research group concentrate on designing and building water-soluble organic "host" molecules that contain hydrophobic receptor sites. They also work on the synthesis of organic molecules with unusual structures in order to create new types of bonds and electronic structures. His quarters, which contain a large computer facility used to model bonding, are in what used to be Crellin.

Also in Crellin is the "big" instrument room, containing the instruments (such as mass spectrometers) that are shared by all members of the chemical synthesis group, which includes, from the inorganic side, professors Fred Anson and John Bercaw, assistant professor Terrence Collins, and Gray. Faculty offices for the organic group (including an office for visiting scholars) will be located all together in Crellin, giving them "places to run into each other." Everywhere in the new lab "getting together, facilitating communication" is emphasized; there's a large common seminar room and a number of smaller meeting rooms. Dividing walls in the laboratories, necessary to cut down on noise, have big windows to make the separation less rigid.

Division chairman Fred Anson will have his office in the east wing (Crellin) — the first-floor, northeast-corner room that originally was Linus Pauling's office when he was division chairman. The first floor will also contain a classroom and a stockroom. It has been exciting to Grubbs to watch it all happen. "At one point a stockroom is just a square drawn on a piece of paper, and then a couple of years later there it is. At Caltech an idea doesn't get lost." □

Beckman Awarded Tolman Medal

On April 24, 1986, the day before the dedication of the Arnold and Mabel Beckman Laboratory of Chemical Synthesis, the Southern California Section of the American Chemical Society awarded its 1985 Richard C. Tolman Medal to Arnold O. Beckman "for the invention and development of instruments that have greatly advanced the frontiers of chemistry."

Nominees for the prestigious award are judged for their achievements in chemistry, significant practical applications of technology, and dedicated service to the profession. Other Caltech recipients include Ernest Swift, Arie Jan Haagen-Smit, James Bonner, John D. Roberts, and Harry Gray.

Of Tolman the ACS local section writes: "His career properly reflects the qualities sought in the recipient of the medal named after him. His interests were extremely broad, and he made outstanding contributions to the development of chemistry in southern California. In addition. he served his nation well, acting in various capacities of national scope and international importance."

Tolman came to Caltech in 1921 as professor of physical chemistry and mathematical physics. Beckman, who had studied under him at the University of Illinois, followed two years later, primarily influenced in that decision by Tolman. The development of chemistry in southern California has clearly benefited from that double migration westward. □