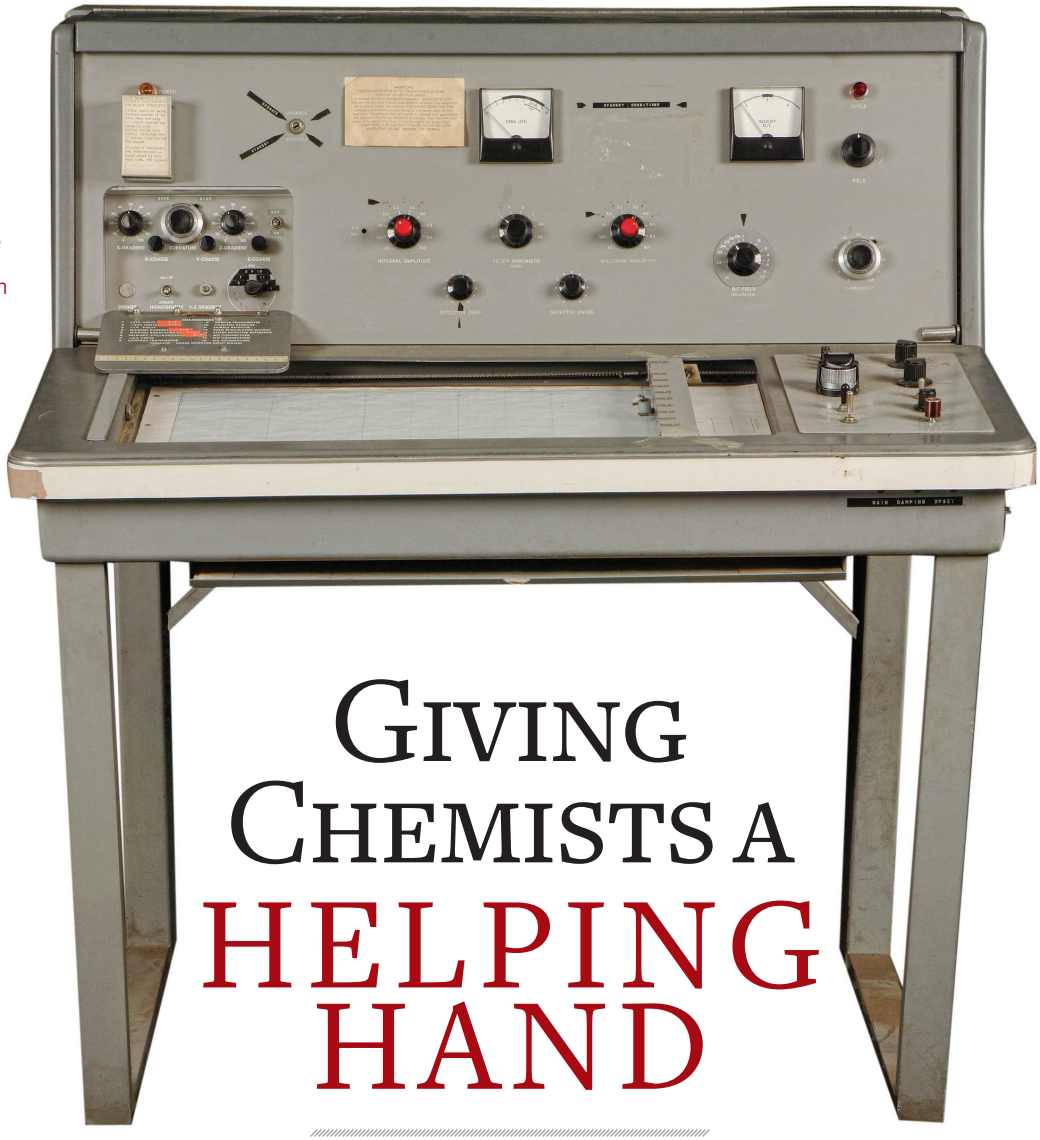

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EARLY BIRD The Varian A-60, the console of which is shown here, was the first commercially available NMR spectrometer.

GIVING CHEMISTS A HELPING HAND

Analytical instruments have answered crucial questions—and given scientists tools to pose new queries

CELIA HENRY ARNAUD, C&EN WASHINGTON

ANALYTICAL INSTRUMENTS OPEN A WINDOW on the chemical world. With them, scientists gain quantitative and qualitative information about how the world works. And as these tools improve, they help researchers work faster and better. Instruments help them answer important questions and provide the means for them to ask new ones they didn't previously know they had.

"In all processes, whether in engineering, science, or medicine, you need quantitative numbers to optimize the goals" of research studies, says Jonathan V. Sweedler, a chemistry professor at the University of Illinois, Urbana-Champaign, and editor of the ACS journal *Analytical Chemistry*. "Medicine and manufacturing are based on literally thousands of analytical tests done by a huge range of analytical instruments." For example, every number in a metabolic profile—say, glucose or cholesterol levels—comes from an analytical test.

"I would argue that none of the work done in chem-

istry after 1950 would have been possible without electronic analytical instruments," says David C. Brock, a research fellow with the Chemical Heritage Foundation who focuses on instrumentation. Analytical instruments have allowed individual researchers to accomplish much more in their careers than would have been otherwise possible, Brock says.

AN EARLY EXAMPLE of such electronic analytical instruments is the pH meter commercialized by Arnold O. Beckman in the 1930s, when he was a professor at California Institute of Technology. He developed the device as a favor for a friend who was looking for a reliable, rugged way to measure the acidity of citrus products.

Beckman's pH meter wasn't the first device used for measuring pH—it wasn't even the first commercial one. But it avoided the delicate glass electrodes used in other setups, and it gathered all the components necessary for measuring pH into a single, portable instrument, a capability that hadn't been available before. National Technical Laboratories, Beckman's company, introduced his pH meter in 1935; the next year the company sold 444 of the devices. In 1937, the company introduced a slightly improved version—the model G, which the company produced until 1964. That simple device was the springboard for Beckman Instruments, now called Beckman Coulter, a unit of Danaher Corp.

"That first NMR machine came only with instructions of how to turn on the magnet."

The pH meter is a relatively simple instrument, but commercialization has helped extend the reach of more complex instruments as well. Take nuclear magnetic resonance, for example.

John D. (Jack) Roberts is old enough to remember organic chemistry before nuclear magnetic resonance spectroscopy. "When I did my Ph.D. research, there were almost no instruments," says the 95-year-old emeritus professor at Caltech. The advent of NMR and other instruments "changed everything," he says.

In NMR, atoms in a magnetic field absorb radiation at radio frequencies. The phenomenon was first measured in molecular beams by Isidor I. Rabi in 1938. In 1944, Felix Bloch and Edward M. Purcell extended it to measurements of liquids and solids.

Before NMR, organic chemists relied on deductive measurements of properties such as melting and boiling point and refractive index to characterize the compounds they made. NMR gave chemists a chance to look more directly at molecular structure—and not just overall structure but the structure of particular parts of a molecule. The "chemical shift" of a proton reveals its chemical environment. Peaks can be further resolved into multiple peaks. Such splitting results from interactions of magnetic nuclei with other nearby magnetic nuclei.

Roberts first heard of NMR in 1950 while he was an associate professor at Massachusetts Institute of Technology. At the time, he

didn't grasp the full potential of the method. A better understanding came a few years later while he was consulting for DuPont. By then, he was on the faculty at Caltech, where Linus Pauling was chair of the division of chemistry and chemical engineering.

"I went back to Pauling and said, 'I've got to have an NMR machine,' " he remembers. "We argued about it for a long time." Roberts finally convinced Pauling when he said that NMR might be able to distinguish between equilibrating species. Caltech thus got its first NMR in 1954. "That first NMR machine came only with instructions of how to turn on the magnet," Roberts says.

Roberts was a pioneer in bringing NMR to organic chemists. NMR was initially used only for proton analysis, but Roberts helped develop it for other NMR-active nuclei such as carbon-13 and nitrogen-15. Analyzing both of these nuclei was more difficult than carrying out proton NMR because of their low abundance and the weak signals they emit.

IMPROVEMENT The Beckman model G pH meter was sold from 1937 to 1964.

Advances in NMR have moved the technique beyond small organic molecules to large biological molecules like proteins, making it a frontline tool in structural biology. And the development of imaging techniques based on NMR has turned it into a medical tool: magnetic resonance imaging.

CHEMISTS AREN'T the only ones to see the need for new tools. "Leading-edge biology always mandates the development of new technologies to explore new dimensions of data space," says Leroy Hood, president of the Institute for Systems Biology, in Seattle.

In his early days as a professor at Caltech, Hood had difficulty convincing his colleagues in biology that he should devote some of his time to developing new tools. In fact, the chair of his department encouraged him to give up technology development. "Senior biologists at Caltech felt it was unseemly to have all this engineering in biology," Hood says.

Luckily for the rest of the biology community, Hood was not deterred. While he was at Caltech, his group continued to develop instruments that in the long run changed biological research—most notably the automated DNA sequencer.

Commercializing the DNA sequencer turned out to be more challenging than Hood had expected. He shopped it and three other instruments (synthesizers for DNA and proteins and a sequencer for proteins) to 19 different companies, including Beckman Instruments. They all turned him down. Instead, he founded Applied Biosystems with the goal of developing the suite of instruments himself.

"I was really lucky none of those other companies took me up," Hood says, because Applied Biosystems was willing to devote the effort and resources needed to develop those instruments. The automated sequencer became the key technology for the Human Genome Project.

But the development of DNA sequencing tools didn't stop there. "Look at the revolution we've seen since we developed the first instrument in the 1980s," Hood says, referring to the increasing ease of obtaining ge-

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netic information that is paving the way for personalized medicine. Applied Biosystems' first-generation capillary-electrophoresis-based sequencers were used to sequence the human genome. Second-generation sequencers were massively parallel sequencing systems made by Illumina and Complete Genomics. Third-generation systems, still in development, are nanopore, nanochannel, and single-molecule electronic detection systems "that I think are going to complete the revolution," Hood says.

And instrument development will continue to advance in the future. In the field of neuroscience, for example, "even with incredible tools, we still don't understand the nature of consciousness, learning, and memory, and how neurons control behavior," Sweedler says. "Tool development has been fantastic, but it's not done." ■

From C&EN Archives

In 1986, Leroy Hood and his coworkers at California Institute of Technology reported the first automated DNA sequencer. This instrument paved the way for the international effort to sequence the human genome. On page 4 of its June 16, 1986, issue, C&EN described the development this way:

The machine, called a DNA sequenator, "is an extremely important advance because [with it] we can begin to think about setting up facilities for the really extensive sequence analysis of human chromosomes," Hood explains. "Such analysis is vital to understanding genetic diseases and cancer because often only subtle differences exist between normal DNA and DNA involved in pathological conditions. To understand these diseases, researchers must discover what these subtle differences are and how they cause illness."

The machine allows automation of many of the tasks of gene sequencing that until now have had to be done laboriously by hand. It likely will reduce both the time and the cost of doing sequence experiments. The commercial instrument, which Applied Biosystems expects to be marketing by the end of this year, will be capable of sequencing 500 DNA unit bases per hour and costs roughly $90,000. Researchers estimate that eventually the cost of determining a genetic sequence by machine will be pennies per base, compared with a present cost of $1.00 to $5.00 per base using manual techniques.

So far, the Caltech researchers have been able to determine the sequence for fragments of DNA several hundred bases long in one run. They expect improvements to allow sequencing of 1,000 base-unit DNA, which is roughly the size of individual human genes.

Since then, the instruments and chemistries used for DNA sequencing have continued to evolve and the price has continued to drop. And, thankfully, the word "sequenator" has been consigned to the linguistic dustbin.