SCIENCE NEWS of the week

Fast X-Ray Flash Produces Results

Cornell University scientists have successfully snapped X-ray diffraction pictures of biological molecules 1 million times faster than ever before, opening the way for studies of how molecules change shape in the instant they perform important functions in the body. The test also proves the design of the X-ray-producing device that is the heart of a laboratory being built to produce X-ray beams 10,000 times brighter than previously possible, a capability that will enable scientists to push forward the study of metals and other materials.

X-ray diffraction is one of the oldest and best methods scientists have for looking at the structure of biological molecules; it was X-ray diffraction that gave clues to the structure of DNA, hemoglobin and other molecules. The benefits of the technique's high resolution have been somewhat offset, however, by the long exposure times necessary to get a good picture. In classical X-ray crystallography, samples in crystalline form must be exposed to X-rays for hours or days, yielding a static view of molecules that have sometimes been damaged by the X-rays themselves. Recently, scientists at the Massachusetts Institute of Technology succeeded in making millisecond X-ray diffraction photographs of proteins (SN: 9/19/87, p.182), but that was still not fast enough to capture the protein's changes in form as they happen.

The Cornell scientists used the new device, called an undulator, to produce a bright flash of X-rays, which enabled them to make X-ray diffraction photographs in one-tenth of a billionth of a second. The researchers think this will allow them to capture changes in such molecules as hemoglobin as it binds to oxygen or the visual pigment rhodopsin when it is struck by light. "There are many important biological processes that occur on this time scale," says Cornell biochemist Keith Moffat.

The new technique still requires the molecules to be in crystalline form. This makes the chemical reaction difficult but not impossible to induce, Moffat says. The crystals have a lot of water in them, allowing molecules to interact freely with each other, and it might be possible to start the chemical reaction with light just before the X-rays are turned on, he says.

The fast exposure time also causes less degradation of the sample because the molecule-destroying free radicals produced by the X-rays don't have time to do much damage, says Wilfried Schildkamp, another researcher on the team.

The device that made all this possible, the undulator, was developed by scientists at Cornell and the Argonne (Ill.) National Laboratory. It will later be used as the principal component of an X-ray study facility being built at Argonne, called the Advanced Photon Source. The undulator won't fit in most biology laboratories, because it requires an electron storage ring to function, such as the half-mile-diameter ring used at Cornell.

Scientists have long used the X-rays produced by such rings when fast-moving charged particles (in this case electrons) are turned by powerful magnets. This "synchrotron radiation" can be intensified by the undulator, which uses many magnets to make the electrons wiggle back and forth 61 times instead of making just a single turn as they do at each magnet in Cornell's electron ring. Also, unlike the broad-spectrum X-rays produced by single magnets, the X-rays emanating from the undulator are "pseudo-monochromatic" and range over only a few wavelengths, says Gopal Shenoy of Argonne.

When the Advanced Photon Source is completed in 1995 it will have 35 undulators, each much more powerful than the experimental model at Cornell. Scientists will use such intense X-rays to probe the structure of many materials, such as metals, meteorites and superconducting ceramics, say the Cornell researchers. "[The undulator] delivered everything it was supposed to and more," says Boris Batterman, director of the Cornell High Energy Synchrotron Source. "It shows that the Advanced Photon Source will be . . . the most versatile source of synchrotron radiation in the world."

— C. Vaughan

First stem cells purified from marrow

Scientists knew where to search, but trying to find stem cells in the bone marrow was like looking for a toothpick in a lumberyard. Though they give rise to the entire blood supply and immune system, stem cells make up only a small fraction of bone marrow cells (0.05 percent in the mouse), and scientists have had only indirect evidence that they exist at all. Now, researchers using refined immunological procedures on mouse bone marrow have succeeded in purifying stem cells for the first time, they report in the July 1 SCIENCE. Similar procedures in humans, though more difficult, might prove helpful in isolating human stem cells and could improve the efficiency and safety of bone marrow transplantation, they add.

Before performing a marrow transplant, doctors check to see that the antigens of the donor's bone marrow closely match those of the recipient's. A mismatch could make the host's immune system reject the donor cells. Since stem cells are only precursors and thus have no antigens that the patient's immune system would recognize as foreign, a stem cell transplantation theoretically would avoid the risk of adverse immune reactions. For this reason, the goal of isolating a pure stem cell population has enticed medical researchers for decades.

To obtain mouse stem cells, Irving Weissman and Shelly Heimfeld of Stanford University School of Medicine in Palo Alto, Calif., and Gerald Spangrude, now at the Royal Melbourne Hospital in Victoria, Australia, sorted types of mouse bone marrow cells by the different antigens on their surfaces. They added antibodies that attached to antigens on certain of the cells, such as red blood cells, B cells or T cells, and then eliminated those cells from the population. To the remaining cells, they applied two other antibodies, Thy-1 and Sca-1, that previous research indicated would bind to stem cells. They saved only those cells that bound to both antibodies.

After the antibody treatment, the researchers injected the selected cells into mice whose bone marrow had been destroyed through irradiation. They then tested the mice for their ability to reconstitute the different blood cell types. The only cells capable of reproducing the mouse's complete blood supply were those that did not attach to the first set of antibodies but did bind to Thy-1 and Sca-1. Weissman and his colleagues also discovered that as few as 30 of these select cells could revive the entire blood supply. "We are very confident that these are all stem cells," says Heimfeld.

Weissman's group is now beginning to explore ways to introduce genes into mouse stem cells. If his team succeeds, its mouse system might serve as a model for gene therapy in humans. Doctors theoretically could remove a patient's stem cells, insert genes needed to correct a genetic defect, and inject the altered stem cells back into the patient, say the researchers. "Now that we have a purified population of stem cells," says Heimfeld, "gene therapy is a feasible technique. It looks very promising."

— M. Hendricks