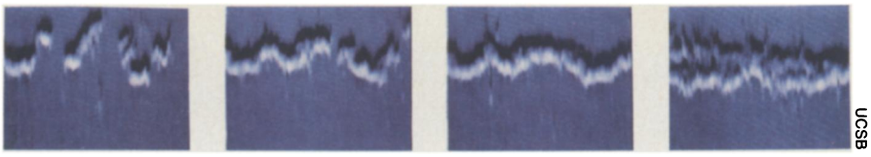
SCIENCE NEWS of the week

Making 'Movies' of Biological Molecules



UCSB

Atomic force microscope captures fibrin polymerizing on mica surface.

In a preview of coming attractions, researchers north of Hollywood have used a new microscope of their own design to make the world's first "movie" of molecular actions underlying a biological event. The microscope will provide one of the clearest windows yet, they say, on the molecular nuances of blood clotting, cell replication and other biological and chemical processes.

In recent years, scientists have been building and using a new family of microscopes — known as scanning probe microscopes — for viewing surfaces at unprecedented molecular and atomic scales (SN: 4/19/86, p.244). The first of these — the scanning tunneling microscope — and a sequel, the atomic force microscope, work by scanning the atomic contours on a sample's surface with a superfine stylus. A computerized feedback mechanism controls the distance from probe to sample, maintaining between the two either a constant tunneling current (for the scanning tunneling microscope) or a constant force (for the atomic force microscope). The computer then can assemble an image of the surface's atomic or molecular landscape.

In the March 24 SCIENCE, nine researchers from Stanford University and the University of California, Santa Barbara, report using a new type of atomic force microscope that is sensitive, fast and gentle enough to image biological molecules even as they act out molecular events. "We have always hoped that the power of scanning probe microscopes could be used to look at biological samples and benefit people," says Paul K. Hansma, the Santa Barbara physicist leading the effort. "We're very excited that now it appears this will indeed be possible."

The heart of the new microscope is a probe made with a tiny, flexible cantilever tipped with a shard from a shattered diamond. Coauthor Calvin F. Quate of Stanford, who helped invent the first atomic force microscope in 1986, supplied the probe. A micropositioner continuously moves the sample underneath the probe, which presses on the surface with a force several million times gentler than the tracking force of a record-player stylus. By moving the sample up or down, a feedback loop keeps the tracking force of the probe constant. A computer interprets these movements as atomic or molecular surface features, which it then assembles into an image.

By scanning in water instead of in air or a vacuum, the researchers can apply and control much more minuscule tracking forces. Earlier designs required using forces that would move and disrupt the sample molecules. The aqueous setting also should enable scientists to study molecules like proteins and DNA in more physiologically realistic conditions.

"This is a startling development," says Quate. Although he and his colleagues have yet to achieve atomic resolution with biological molecules, Quate says that replacing the diamond stylus with an even more sensitive, single-piece probe now being designed could do the trick. The scientists already have used their microscope to image rigid materials such as mica at atomic resolution and biological molecules such as polyaniline (a protein-like polymer built of amino acids) at nearly atomic resolution.

But the most striking application so far has produced a moving image of the protein fibrin as it polymerizes into a sheet. In the body, fibrin molecules emerge from a parent blood protein, web together and initiate blood clots. "Further research will be aimed at seeing the mechanisms of new clot-dissolving drugs," Hansma told SCIENCE NEWS. In addition, since the microscope works in water, it can be used to image numerous systems ranging from "mitochondria in cytoplasm to painted ships in seawater," he and his colleagues suggest in their report.

"It is the first time that you can look at biological samples in real-time at that resolution," remarks physicist and scanning probe microscopist Kumar Wickramasinghe of IBM's Thomas J. Watson Research Center in Yorktown Heights, N.Y. Adds Daniel Rugar, another scanning probe microscopist at IBM's Almaden Research Center in San Jose, Calif., "It's showing that the atomic force microscope has real potential to observe ongoing chemical processes." — *I. Amato*

Early alcoholism: Crime, depression higher

Researchers studying a large sample of male alcoholics say those whose drinking problems emerge before age 20 are much more likely to experience clinical depression, attempt suicide and spend time in jail for crimes involving physical violence. The behavior of this "subgroup" of alcoholics is apparently influenced by disruptions in the availability of serotonin, a chemical messenger in the brain involved in mood and aggression, maintain psychiatrist Laure Buydens-Branchey of the Veterans Administration Medical Center in New York City and her colleagues.

The findings, reported in the March ARCHIVES OF GENERAL PSYCHIATRY, support a theory proposed by C. Robert Cloninger of Washington University in St. Louis (SN: 7/30/88, p.74). Based on a study of Swedish adoptees, he suggests two types of predisposition to alcoholism. Type 1, the more common, first appears among people in their late 20s or older and is heavily influenced by environmental factors. Type 2 is less affected by the environment, usually surfaces during adolescence and is accompanied by violent and impulsive behavior.

The New York researchers tested Cloninger's theory in a study of 218 men admitted to an alcoholic rehabilitation clinic. The sample was split according to age: 66 men reported excessive drinking beginning before age 20, while 152 said alcohol abuse began later on.

Patients who started abusing alcohol in their teens were twice as likely to have spent time in jail for violent offenses, three times as likely to have suffered depression and four times as likely to have attempted suicide as patients whose alcoholism began after age 20. Individuals in the younger group also were more likely to have alcoholic fathers.

Patients whose alcoholism began early and who had histories of depression, violent behavior or both also had markedly lower blood levels of tryptophan shortly after withdrawal from alcohol, the researchers note. Tryptophan is an amino acid involved in serotonin production.

As others have proposed, these patients may have a preexisting serotonin deficit that worsens with years of excessive drinking, the scientists say. This, in turn, may contribute to recurrent depressions or violent episodes.

The next step, they add, is to test drugs boosting tryptophan or otherwise modifying serotonin in individuals whose alcoholism appeared during adolescence.

— *B. Bower*