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COVER: Honda's stratified charge CVCC engine and Mazda's Wankel rotary engine coupled with a thermal reactor are leaders in the quest for automobiles that can meet provisions of the Clean Air Act. Other technological approaches are being given renewed emphasis as well. See p. 276.

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Subscription Department
231 West Center Street
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Subscription rate: 1 yr., \$10; 2 yrs., \$18; 3 yrs., \$25. (Add \$2 a year for Canada and Mexico, \$3 for all other countries.) Change of address: Four to six weeks' notice is required. Please state exactly how magazine is to be addressed. Include zip code.

Printed in U.S.A. Second class postage paid at Washington, D.C. Established as Science News Letter in mimeograph form March 13, 1922. Title registered as trademark U.S. and Canadian Patent Offices.

Published every Saturday by SCIENCE SERVICE, Inc., 1719 N St., N.W., Washington, D.C. 20036. (202-785-2255). Cable SCIENSERV.

april 28, 1973

Double helix at the atomic level

Atomic details of nucleic acids have been visualized

The genetic material of life, DNA and RNA molecules, is shaped like spiraling staircases or double helices. Francis Crick and James Watson deciphered the structure of DNA exactly 20 years ago and received a Nobel Prize for the work. Subsequently they and other investigators determined that RNA molecules have structures identical to DNA, but with one chemical variation. Determining the structure of DNA and RNA was one of the major biological advances of the century. Current research in molecular biology is based on the proposed structure, and most findings indicate that it is correct.

Crick and Watson knew from available chemical evidence that the backbones of each DNA molecule are made of sugar and phosphate molecules. By studying the X-ray diffraction patterns exhibited by fibers of DNA, they could see some of these sugars and phosphates coiled or spiraling. They also knew from available chemical evidence that the steps, that is, bases of the

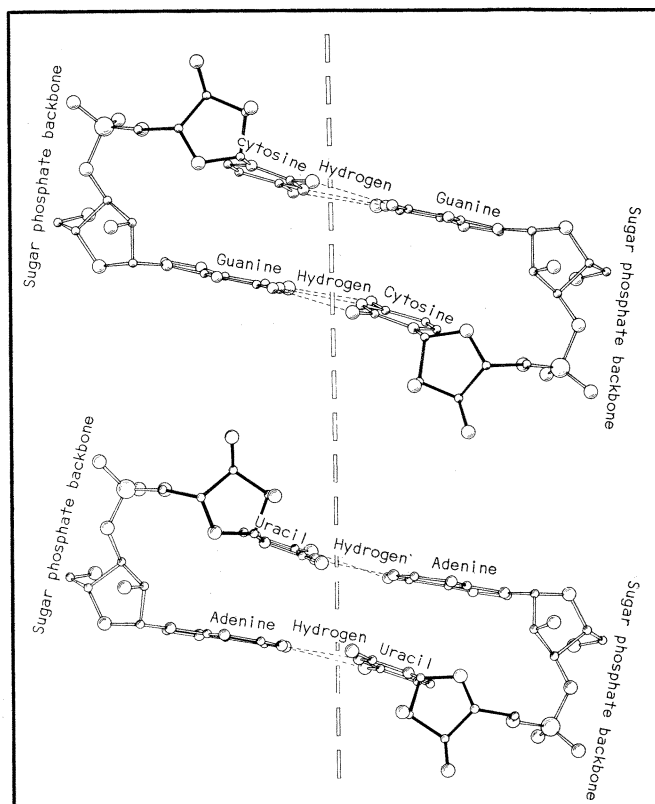
spiraling DNA staircase are made of four kinds of chemical molecules—adenine, thymine, guanine and cytosine. They could not see the details of the steps, though. But by ingenious calculations they figured out how the steps are put together. One step consists of a pair of adenine and thymine, say, the next step consists of a pair of guanine and cytosine, the next is a pair of adenine and thymine, and so on, pairs of adenine and thymine and pair of guanine and cytosine alternating up the spiral staircase. In each step, adenine and thymine or guanine and cytosine are held together by hydrogen bonds. Subsequently RNA was found to have the same structure—spiraling bannisters of sugars and phosphates, with steps of four kinds of molecules, except that uracil substitutes for thymine.

The X-ray diffraction techniques available to Crick and Watson and to other investigators to determine the double helical structure were limited:

Two steps of cytosine bonded by hydrogen to guanine, and flanked by two bannisters of sugars and phosphates (top).

Two steps of uracil hydrogen-bonded to adenine, also flanked by two backbones of sugars and phosphates.

Rich et al, MIT



First successful enzyme therapy in humans

Previous attempts to give enzyme injections as therapy for enzyme-deficiency diseases haven't worked. The enzymes were not pure enough, or they could not get through the "blood-brain barrier" to the brain. This barrier keeps foreign chemicals from entering the central nervous system. Enzyme was given to a child with the enzyme-deficiency disease called Tay-Sachs, for example. But it did not help the child because it was needed in the brain and could not enter the brain from the bloodstream.

Now an attempt at enzyme therapy appears finally to have been successful. It was reported by Roscoe Brady, a physician and biochemist at the National Institute of Neurological Diseases and Stroke, last week at the annual meeting of the Federation of American Societies for Experimental Biology in Atlantic City.

Fabry's disease, an inherited condition, is transmitted from mother to son. Some 150 men in the United States are estimated to have the condition. As teenagers they experience severe pains in their arms and legs. They usually die in their early forties from poisoning of the kidneys by excessive fats. In 1967 Brady and his colleagues identified the cause of the disease—a faulty fat-metabolizing enzyme called alpha galactose sidase. Because the abnormal enzyme does not break down lipids in the blood

as it should, they accumulate in the body. Brady and his team tried to purify the enzyme in its normal form from human placental tissue.

Four months ago they got enough of the enzyme to inject into two patients with Fabry's disease. It has been about three months since the patients received the single injection of enzyme. The results look promising—a reduction in fats transported from the bloodstream to the kidneys. Brady does not know whether the normal enzyme also reaches fats already in the kidneys. "We can slow the disease," he says. "I am not sure we can reverse it."

The normal alpha galactose sidase contains 200 amino acids. Its sequence has not been determined. Until it is, the enzyme cannot be synthesized. Obviously if a synthetic enzyme can be made, therapy would become available to many more persons with Fabry's disease. Brady worries, though, that a synthetic enzyme might not help patients as well as the natural enzyme appears to do.

Brady and his co-workers have also just purified a normal version of the enzyme glucose cerebrosidase. The abnormal form of the enzyme metabolizes fats inadequately in persons with Gaucher's disease. Brady anticipates that when he and his group purify enough of the normal enzyme it can be used to treat persons with the condition.

The diffraction patterns of fibers of DNA and RNA die out at resolutions finer than three angstroms. So they could not see the molecular architecture of the double helix very well. However, in the past few years scientists have learned how to submit single crystals of fragments of DNA or RNA to X-ray analysis. This technique allows the fragments to be seen at the atomic level.

A group of crystallographers and physical chemists at the Massachusetts Institute of Technology have now used the newer technique to see, in RNA, steps of adenine and uracil and steps of guanine and cytosine. These are the first crystal structures, report the scientists, "in which the atomic details of the double helical nucleic acids can be visualized." The investigators are Alexander Rich, John Rosenberg, Nardrian Seeman, Jung Ja Kim, F. L. Suddath, Hugh Nicholas and Roberta Day.

Part of the MIT researchers' findings were published in the March PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES. The rest is in press with NATURE. They also reported their work last week at the annual meeting of the Federation of American Societies for Experimental Biology in Atlantic City.

In an interview at the FASEB meeting, Rosenberg and Seeman explained that they first grew crystals of RNA molecules for X-ray diffraction studies. This was tricky. When they got good crystals, they used X-ray diffraction, linked with a computer, to help bring the atomic makeup of the crystals into focus. As Rosenberg recalls, "It was like having 5,000 knobs on a television

screen and having to diddle with the knobs to bring the picture into focus." They finally saw, in the crystals, steps of adenine hydrogen-bonded to uracil and steps of guanine hydrogen-bonded to cytosine. They also got some surprises, such as seeing a sodium ion next to a step of adenine and uracil. Rosenberg and Seeman believe that series of ions like the sodium ion may run through the steps of the spiraling RNA or DNA staircase and provide recognition points for proteins that interact with them. Virtually nothing is known about protein recognition of DNA or RNA, at least at the atomic level. □

Bells, brains and memory molecules

In recent months George Ungar, a pharmacologist at Baylor College of Medicine, and his colleagues, have ruffled the biological world by claiming the first isolation of a "memory molecule." It is a protein, isolated from the brains of rats trained to fear the dark. When the protein is injected back into the brains of untrained rats, it purportedly makes them afraid of the dark. Ungar and his team named their protein "scotophobin," after the Greek for "fear of the dark."

Because of the vast impact such a claim could have on brain research, learning, teaching methods and other areas of human life, Ungar's scotophobin has been heavily questioned by other scientists. Several issues of the prestigious scientific journal NATURE have devoted considerable space to Ungar's evidence for scotophobin and to other scientists' criticism of his research (SN:

8/12/72, p. 100; 3/24/73, p. 180).

Now Ungar has come up with more fuel to strengthen his case for memory molecules. His latest evidence is for other kinds of memory molecules than scotophobin. In reporting these findings last week at the annual meeting of the Federation of American Societies for Experimental Biology, Ungar declared, "The best way to dissipate misunderstanding [about memory molecules] is to isolate more of the substances."

During the past two years he and his colleagues have trained some 6,000 rats to ignore the sound of a loud bell, then collected their brains. The brain material was submitted to a series of purification steps. At each step the fraction containing the active memory material was identified by its effect on mice. In other words, the active material was identified when its injection into the brains of mice caused them to ignore the bell. Control mice did not ignore the noise. After passing the active material through six steps of purification they obtained a pure substance. It turned out to be a protein, like scotophobin, but of different size and different amino acid composition.

They have also obtained, in a highly purified state, two proteins that were formed in the brains of fish trained to avoid two different colors. The two substances corresponding to the two avoidance behaviors are proteins about the size of scotophobin but with different chemical compositions. They are also purifying a substance formed in the brain of goldfish trained to adapt their swimming to the adverse conditions created by a float attached to them. □