Bind-and-snip search for Z-DNA

Scattered throughout chromosomes are stretches of DNA that twist jaggedly to the left rather than spiraling smoothly to the right. Since the discovery of this zigzagging Z-DNA six years ago, scientists have speculated that it plays a role in control of gene activity. Now research with special metal complexes has pinpointed Z-DNA sites in chromosomal positions near the ends of genes — sites where the Z-DNA is likely to exert gene control. A metal complex that binds, and also cuts, Z-DNA may provide a valuable tool for snipping chromosomes into single-gene pieces.

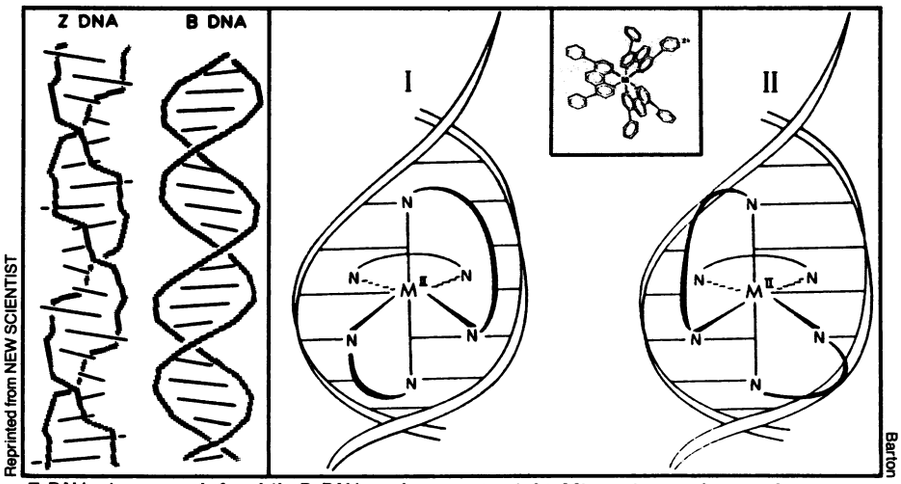
The DNA-distinguishing complexes are octahedral compounds that have mirror-image forms resembling either a right-handed or a left-handed propeller. The right-handed form nestles into grooves of the right-handed helix of normal double-stranded DNA (called B-DNA), but the left-handed form just doesn't fit. However, the left-handed complex is better than its mirror image at binding to the left-twisting Z-DNA.

The behavior of these complexes depends in part on the central metal atom, says Jacqueline K. Barton of Columbia University in New York City, who has been selected to receive the National Science Foundation's Alan T. Waterman Award, given annually to a young scientist. When Barton constructs the complexes with ruthenium at the center, she can easily measure how much attaches to DNA, because binding enhances its luminescence. Better still, if the metal is cobalt, the complex cleaves a bound Z-DNA strand when it is exposed to light. This reaction allows Barton and colleagues to determine the precise location of Z-DNA segments by measuring the lengths of the resultant pieces.

"We find Z-DNA associated with the ends of genes," Barton told SCIENCE NEWS. "It is a conformational punctuation mark in the control regions."

Barton first looked at a ring of DNA used in genetic engineering (the plasmid called pBR322) and found four Z-DNA sites, each located about 20 base pairs outside a gene or at a special control region, the origin of replication. Next she examined the animal tumor virus SV40, as a model for the DNA of complex organisms. "The correlation [between Z-DNA and the ends of genes] is holding up very, very nicely," she says.

Other researchers have also located Z-DNA in regions that control DNA activity. One of the Z-DNA sites Barton identified on pBR322 corresponds with a site other scientists identified using an antibody that binds to Z-DNA. Alexander Rich of the Massachusetts Institute of Technology, who first discovered Z-DNA (SN: 12/22 & 29/79, p. 420), reports binding in an SV40 control region by proteins that attach selectively to Z-DNA. Such proteins have been found in many organisms, including humans, fruit flies, wheat and yeast, Rich told a recent seminar in San Diego of the American Cancer Society.



Z-DNA zigzags to left, while B-DNA corkscrews to right. Mirror-image forms of a propeller-shaped metal complex (inset) bind selectively to different conformations of DNA. Right-handed complex (I) fits into B-DNA better than does its mirror image (II).

In addition to its role in analyzing Z-DNA, Barton's octahedral cobalt complex may become an important tool in biotechnology. Molecular biologists now use enzymes, called restriction enzymes, to break DNA at specific sites. These sites correspond to different short sequences of nucleotides that have no other known biological importance. It is as if the collection of world literature were broken into volumes not by story but rather whenever particular sequences of common words appeared. However, if the cobalt complex is shown to cut consistently at the ends of genes, it may provide scientists with just the segments of DNA they most desire. Then "libraries" of DNA segments could be comprised of "books" that each contain a complete tale. —*J. A. Miller*

Radiation therapy for arthritic joints

Gold compounds and the antibiotic penicillamine are traditional treatments for rheumatoid arthritis, the joint-destroying disease in which white blood cells and their immune system products invade human joints and cause inflammation. Stanford University researchers now report that high-dose irradiation of lymphoid tissues, such as the spleen and lymph nodes, may be an effective treatment in patients for whom traditional treatments have failed.

White blood cells normally circulate in the bloodstream and in lymph, the transparent fluid collected from body tissues that eventually empties into the bloodstream. The cells leave the blood and lymph and enter body tissues only when viruses or other foreign substances invade the body. But in rheumatoid arthritis, the cells accumulate in the delicate synovial membrane that surrounds joints. The membrane normally allows bones that meet at a joint to move smoothly over each other, but in arthritis, it is inflamed and causes pain when the joint is moved.

Scientists do not yet know why immune cells accumulate in arthritis-diseased joints (SN: 9/4/82, p. 156). They speculate that a virus or a genetic defect in the immune system might be the trigger, causing cells to congregate in joints.

In the present study, reported in the April ANNALS OF INTERNAL MEDICINE, 24 arthritis patients for whom gold compounds and penicillamine treatments had failed were given — over six weeks — either high-dose (2,000 rad) or low-dose (200 rad) total lymphoid irradiation. Neither patients nor observers knew which patient received which treatment. Morning stiffness, joint tenderness, joint swelling and a composite of these factors were measured in each patient.

Patients in the high-dose group showed significant improvement compared with the low-dose group in all four variables at both three and six months after the treatment ended. Patients in the low-dose group showed little improvement, but Samuel Strober, an author of the study, cautions that the small number of patients in this group (11) may have been the reason the researchers did not see significant improvement.

Patients who received high-dose irradiation had side effects ranging from fatigue and hair loss to severely low white blood cell count, according to the report. But the side effects are limited, Strober says, to the six-week treatment period and shortly thereafter. Patients are then maintained on aspirin. Traditional therapies, he says, must be given for the rest of the patient's life, creating longer-term side effects.

—*D. D. Bennett*