Docking of Soyuz 4 and 5 in January.

carry out scientific experiments, engineering studies and applications work. They would serve as laboratories for long-term biomedical studies, for instance, observing the effects on man and animals of long exposure to orbital conditions.

Not all scientists are convinced of the efficacy of conducting scientific studies from manned orbital stations. Between sessions this week at a symposium on the space program at the National Academy of Sciences' fall meeting at Hanover, N.H., Dr. John W. Findley of the National Radio Astronomy Observatory confessed to having mixed emotions about using manned space stations as scientific tools.

Their use as vehicle assembly points and way stations for longer expeditions is sensible, he said, but the inevitable small wobbles in the orientation of the station due to the crew's activity would be likely to make certain precise kinds of physical observations difficult.

The first launch of a small U.S. orbital station, in the Apollo Applications Project, is now scheduled for July 1972. A 60-ton station will support three men for four weeks and then be revisited twice by three-man crews who might stay up to two months at a time. The AAP station will be established inside the empty fuel tank of a giant Saturn 5 rocket stage which will be outfitted with scientific equipment, two decks, several compartments and an airlock and docking module.

The AAP program, which has met many funding delays, has now had its financing restrictions lifted, and, says its director, William C. Schneider, "We're moving full bore ahead." As for the three Soviet Soyuz craft orbited this week, Schneider observes that they are smaller than the planned initial U.S. station. "But if you dock enough of them together you get a very respectable hunk of hardware in orbit." □

THYMINE DIMERS

Repairing the DNA

An abnormal bulge in a strand of DNA has become a unique link between geneticists studying the molecular biology of genes and researchers more directly concerned with clinical effects of inherited disease.

The bulge occurs when two adjacent chemical components of DNA—thymine bases—are struck by ultraviolet light, causing them to fuse into what is called a thymine dimer (see p. 352). This double molecule causes unusual rigidity in the DNA strand, twisting the DNA helix out of shape and preventing the normal process of replication.

Using mutations of this kind in laboratory experiments, Dr. Arthur Kornberg and his co-workers at Stanford University in Palo Alto have formulated a hypothesis to explain the way cells repair defects in DNA.

Simultaneously, Dr. James E. Cleaver of the University of California Medical Center in San Francisco is exploring the possibility of genetic engineering as a cure for a rare genetic defect called xeroderma pigmentosum. The condition is marked by an extreme sensitivity to the ultraviolet light in sunlight, leading almost inevitably to fatal skin cancer. The defect, Dr. Cleaver finds, lies in the patient's inability to repair thymine dimers when they occur, thus allowing the undesirable mutations in DNA to persist.

To understand how cells proliferate, how viruses reproduce and how to promote or suppress these events, Dr. Kornberg says, it is essential to know the mechanism by which DNA is copied and how healthy cells repair it when it is defective. Addressing the annual meeting of the American College of Surgeons in San Francisco last week, the Nobel laureate explained his hypothesis of DNA repair which he calls a cut, paste and seal operation.

The system depends on the activity of three enzymes, studied in Psi x 174 viruses because of their genetic simplicity. The first, as yet unidentified specifically, belongs to a class of proteins called endonucleases. Theoretically, an endonuclease is constantly at work, patrolling strands of DNA, looking for chemical errors. When it finds a bulging thymine dimer, introduced by ultraviolet light, it nicks the DNA strand, thereby signaling another enzyme that something is awry. This second molecule, DNA polymerase, then excises the mutant segment, replacing it with a normal unit of DNA. Finally, a joining enzyme, ligase, pastes the new segment into place, restoring the strand of DNA to a normal state.

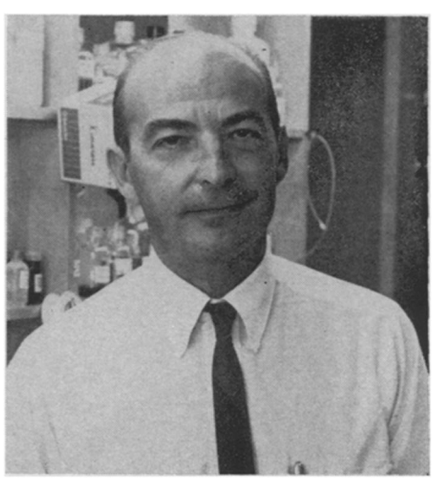
Previously, Dr. Kornberg, who won the Nobel Prize for his work on DNA polymerase, theorized that this enzyme is vital to the process of DNA replication. And, by understanding of the joining properties of ligase, he was able, in 1967, to synthesize the first biologically active molecule of viral DNA (SN: 12/30/67, p. 629).

The role of DNA polymerase in repair, he declares, was unexpected. "I'm really surprised at how much more work this enzyme can do than we ever knew when we started working with it. It is absolutely essential for the survival of life . . . governing the reproduction of genes and repairing them when they are damaged." He concedes that it might perform other tasks as well, but if so, they remain to be identified.

While emphasizing that this explanation of biochemical events surrounding the synthesis of DNA is conjectural, Dr. Kornberg believes the preliminary evidence is strong. In addition to test-tube experiments and chemical analyses, an electron micrograph showing DNA polymerase actually sitting on a strand of DNA clearly confirmed the relationship between the two.

The coincidental result of Dr. Kornberg's and Dr. Cleaver's work is a rare example of basic research developing information needed by a clinical researcher, at the time the need develops.

In the human disease related to Dr. Kornberg's line of research, the inability to excise and repair thymine dimers apparently results from the absence of one of the enzymes active in the repair process. It is most probably the endonuclease, though Dr. Cleaver says he cannot be certain yet. He is sure, however, that the inherited deficiency specifically involves the repair of thymine dimers, because tests



Stanford University

Dr. Kornberg: Cut, paste and seal.

of cells from patients with xeroderma pigmentosum show they are able to mend other DNA damage, such as a clear-cut break in the strand of chemical bases. Such breaks could be identified without the aid of an endonuclease.

To test the possibility of genetic engineering, Dr. Cleaver now plans to take cells from xeroderma patients, grow them in the laboratory and infect them with the SV-40 virus, an agent known to cause cancer in animals but thought to be harmless in man. In the process of infection, the SV-40 virus will empty its DNA into the nucleus of a xeroderma cell, thereby giving it a transfusion of genes. In this case, the virus is merely the vehicle for transporting the new DNA because it is able to penetrate the nuclear membrane and get into the nucleus of the cell.

Hopefully, the deficient cell will incorporate the viral DNA into its own genetic machinery and use the information it contains to make the endonuclease it cannot produce on its own. Preliminary experiments with hybrid man-mouse cells (SN: 10/11, p. 323) and with viruses show this may be possible, but whether the effect would be long-lasting and whether the deliberate introduction of viruses into a human being is safe are questions that have yet to be answered. □

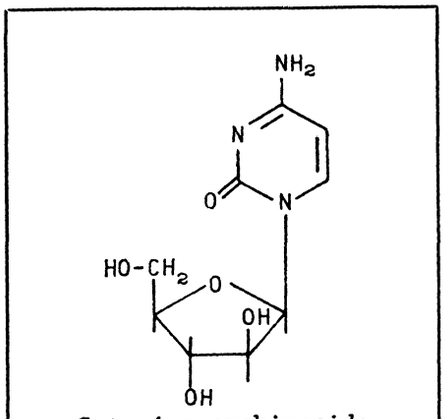
LEUKEMIA

A stronger arm in the arsenal

During the past several years, drug therapy has been the most effective mode of treatment for acute leukemia in both adults and children (SN: 12/21, p. 626). These anticancer drugs act against cells during their reproductive cycles, one cycle of which is DNA synthesis. By inhibiting this synthesis, the production of leukemic white blood cells causing the disease can be halted.

Recent results in humans show that a drug, cytosine arabinoside, that acts during this cycle, but in a different way than previous drugs, may be the most promising in this arsenal to date. Clinical studies show that the drug induces complete remissions of acute granulocytic leukemia in adults and acute lymphocytic leukemia in children in from 40 to 60 percent of patients, for up to periods of 18 months. This remission rate is both higher and of longer duration than any drug used thus far. Although the drug is not a cure, the results of human tests are regarded as more than satisfactory and have elated cancer specialists.

With leukemia, white blood cells proliferate uncontrollably—probably a result of cancerous mutation of the cell. Cytosine arabinoside destroys these cells in their reproductive stage by preventing the conversion of cytidine to deoxycytidine, a chemical component which is necessary for the synthesis of new DNA and therefore new white cells.



Cytosine arabinoside

Formula for a more specific fighter.

Other antileukemia drugs which inhibit DNA synthesis act by a different pathway. They inhibit as well the synthesis of RNA and, in some cases, proteins, which are synthesized prior to DNA. Such inhibitions limit the usefulness of these drugs because both leukemic and normal cells are destroyed by them. A drug that zeros in on the DNA phase is more selective, singling out mainly the weaker leukemic cells for destruction.

The National Cancer Institute, which conducted most of the clinical studies done with cytosine arabinoside, reported that of 184 patients with acute leukemia—both adults and children—the drug induced complete remissions in 69, giving an overall remission rate of 37 percent. And Dr. Emil Freireich, chief of experimental hematology at M. D. Anderson Hospital in Houston, reported complete remissions in up to 56 percent of patients. When the drug was given in combination with other drugs to patients under 30, an overall remission rate of 80 percent was obtained. Dr. Freireich calls cytosine arabinoside a "whole new direction in cancer treatment."

According to Dr. Freireich, the drug has two other advantages: It can be given in large doses because of its relatively low toxicity, and though it does deplete bone marrow, it shows few side effects on other parts of the body.

Information on cytosine arabinoside was presented last week at an all-day conference on the drug called by the National Cancer Institute. Dr. Gordon Zubrod, scientific director for chemotherapy at NCI called the meeting an "experiment in communications." He used the Food and Drug Administration's approval of the Upjohn Company's application on the drug as a way to wave a research success in the face of the budget cutters (SN: 9/20, p. 236).

Development of the drug was the result of cooperation involving Federal Government, industry, universities and independent research institutions. The Chemotherapy Program of the NCI, established by Congress in 1955, allows the Government to help develop new drugs where the profit potential is too small to stimulate the pharmaceutical industry. In the case of cytosine arabinoside the production costs were so high—originally $57 per gram—that more extensive clinical studies were precluded.

Other than NCI and Upjohn, the project included the Sloan-Kettering Institute for Cancer Research, Roswell Park Memorial Institute and the Henry Ford Hospital in Detroit. In addition, grants for research were provided by the American Cancer Institute.

Dr. Saul A. Schepartz, associate scientific director and chief of the Cancer Chemotherapy National Service Center at NCI, said that "perhaps 1,000 patients have been treated with the drug, and the cost for clinical studies has well exceeded $1 million." □

HEAVY-ION ACCELERATORS

The cry from the South

Nuclear physics has always been a major subject of study at Oak Ridge National Laboratory. The laboratory was founded to contribute to the development of the nuclear bomb. Since World War II, it continued to build on the base established in the 1940's, stressing the study of the atomic nucleus in its pure scientific and its practical aspects in nuclear physics, nuclear chemistry and radiation biology.

The laboratory's cooperation with Southern universities has helped to build up a regional constituency in these fields, many of whose members work at universities that were hardly known for scientific research before the war.

But while Oak Ridge was building up its capabilities in nuclear sciences, other national laboratories went after the new field of particle physics, and others—like Brookhaven, Argonne, Lawrence Radiation Laboratory—were the ones that got the big new particle accelerators. "We think the Southern part of the country has been underprivileged in these large accelerators," says Dr. Arthur H. Snell, assistant director of Oak Ridge, and an effort is being made to redress the balance. The vehicle is an accelerator proposal for nuclear, not particle physics.

After existing in something of a