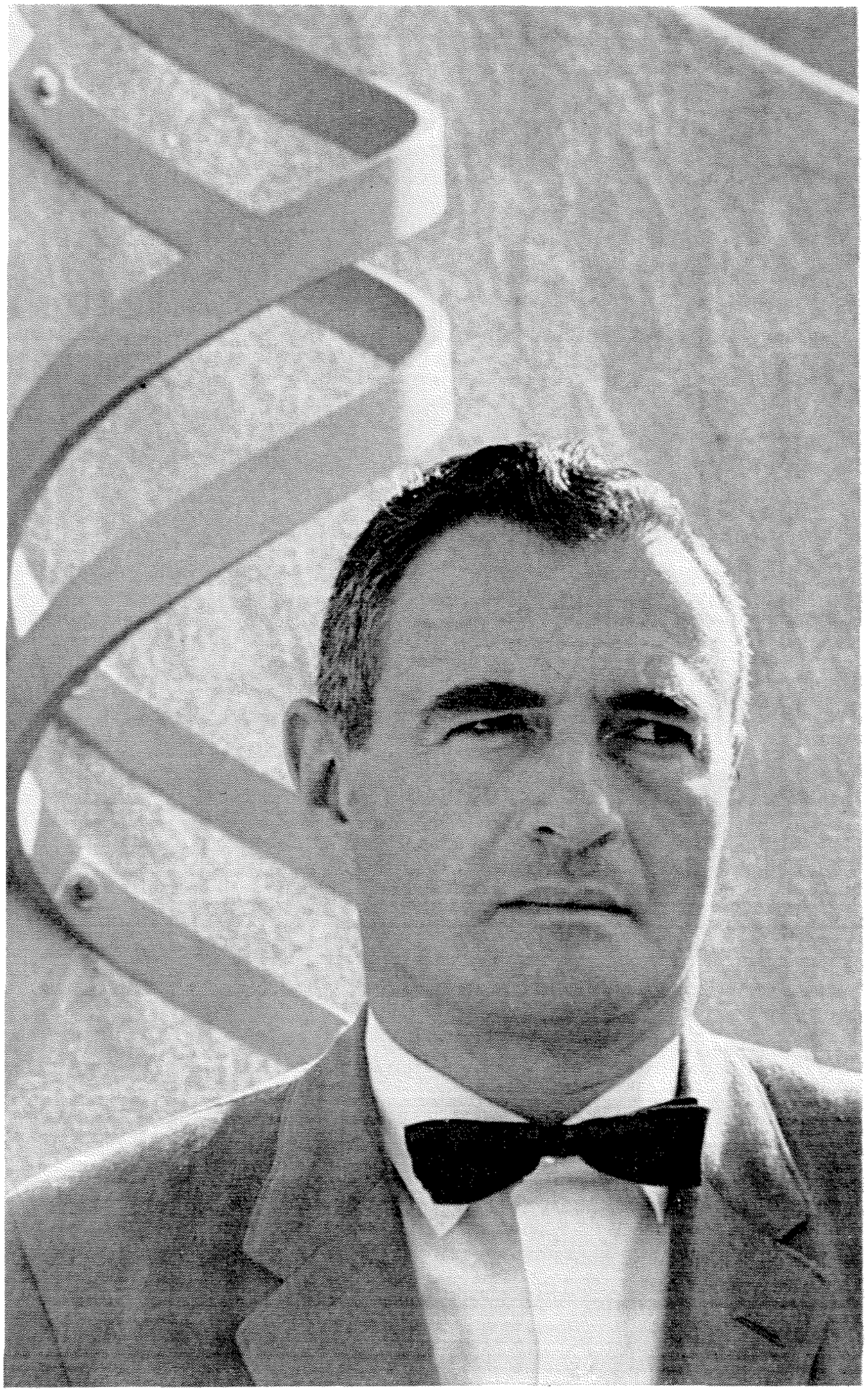

DNA – A PERFECT COPY

Scientists at Stanford University and Caltech collaborate to produce DNA in the laboratory.

"The dramatic advances in molecular biology of the past few decades have laid bare the essential molecular mechanics of inheritance, and of the processes of cellular function and control. . . . In so doing, a secure base has been laid for further advances in our understanding of development and physiology and pathology—a base that can only be compared in this century with that which quantum mechanics provided for the development of modern physics and chemistry. And with this understanding will come the potentiality for intervention and the intelligent control of processes that have known only the mindless discipline of natural selection for two billion years."

—Robert L. Sinsheimer

DNA, the chemical material that controls the hereditary characteristics of every living thing, has now been successfully synthesized in the laboratory. Scientists at Stanford University and Caltech announced last month that they had produced a copy of the DNA of a virus that displays the full biological activity of natural DNA in living organisms; the synthetic DNA can infect bacteria and reproduce itself just as the natural virus does.

This is probably as close as anyone has yet come to creating life in the laboratory. The discovery should not only lead to better understanding of how viruses are duplicated when they enter cells, but also to new knowledge of what takes place when normal cells are changed into cancerous ones.

The team of scientists who collaborated on this research includes Arthur Kornberg, professor and executive head of the department of biochemistry at Stanford; Mehran Goulian, former postdoctoral fellow at Stanford, now on the faculty of the University of Chicago; and Robert L. Sinsheimer, professor of biophysics at Caltech.

Dr. Kornberg shared the Nobel Prize in 1959 for producing DNA from a mixture of inert chemicals. This synthetic DNA had all the physical and chemical properties of DNA found in nature, but it was not biologically active.

The DNA that has now been produced by the Stanford and Caltech scientists is a copy of the DNA of a natural virus known as Phi X 174, which attacks intestinal bacteria. Dr. Sinsheimer is a leading authority on the nature and behavior of this virus, which he discovered some 10 years ago.

Phi X, like all viruses, survives by attacking and infecting a cell that is thousands of times larger than it is. The cell in this case is the bacterium, *E. coli*, a common intestinal microbe. Phi X forces its DNA through the cell wall of *E. coli*, then directs the cell's metabolic machinery to manufacture almost 200 complete Phi X viruses within less than a half hour. The cell soon ruptures, freeing the viruses to attack other *E. coli* cells.

Using methods developed by Dr. Sinsheimer for growing and isolating DNA from Phi X, the Stanford researchers started by taking single rings of natural DNA from this simple virus, which consists of a DNA molecule surrounded by a protein sheath.

The rings were placed in a compatible solution simulating that of the interior of an *E. coli* cell. The solution was rich in the four chemical compounds called nucleotides, which are the basic building blocks of DNA. It also contained two enzymes which proved to be essential in carrying out what scientists know to be the first step in the infective process of this virus in nature. One of them, DNA polymerase, catalyzed the coupling of nucleotides in the building of the new DNA chain, using, at first, the natural viral DNA ring as a template. The second enzyme, DNA ligase, served the special function of closing the chain into a ring.

There were four major stages in the research. The ability of the Phi X DNA to replicate was tested at each stage and at several steps in between. Because DNA synthesis provides a complementary, or mirror-image, copy instead of an exact one, it was necessary to proceed through the several stages to achieve an artificial synthesis of the exact replica of the original, natural DNA ring.

The intensive phase of the research covered three and a half months during which the Stanford scientists, Dr. Kornberg and Dr. Goulian, induced the synthesis of various versions of the DNA of the virus, froze the samples to preserve them, and shipped each succeeding version to Dr. Sinsheimer at Caltech. He then carefully tested the ability of the DNA samples to replicate the complete viruses.

When the final version of the artificially produced DNA was put into living cells, they became infected just as they would from a normal virus. The viruses produced by the infected cells are indistinguishable from natural ones, and they infect in the same way.

The research represents an important step forward in understanding how viruses are duplicated when they enter cells and how DNA polymerase or similar enzymes make new DNA.

"If we know how to use this enzyme to copy this particular virus, then we can copy other viruses," says Dr. Kornberg. "And we can copy them in ways in which we can modify their structure by putting in alternative or fraudulent building blocks to create new forms of the virus. We can then use the synthetic virus to infect cells and produce altered responses."

"It opens a wide door to new discoveries in fighting disease and building healthier lives for mankind."

One possible future application is controlling certain forms of cancer. For example, DNA found in polyoma virus produces a variety of cancers in many animals. "I think it is reasonable to expect that the polyoma viral DNA will be synthesized by an enzyme system," Dr. Kornberg says. "With such a synthetic system we should be on our way toward figuring out what genes in the virus are responsible for the cancer response."

Another possibility in the far-distant future might be the careful manipulation of laboratory synthesis of DNA as a means of modifying genes.

The research has proved two things, according to Dr. Sinsheimer. First, it determined that there are two enzymes, DNA polymerase and DNA ligase, that carry out the first step in the infective process.

Second, considering that there are 5,500 nucleotides in the viral DNA, the work also demonstrated that the copying of the DNA blueprint in the test tube must have been very good. There could not have been many mistakes.

"It is an awesome accomplishment," President Johnson has said of this research. "It opens a wide door to new discoveries in fighting disease and building healthier lives for mankind."