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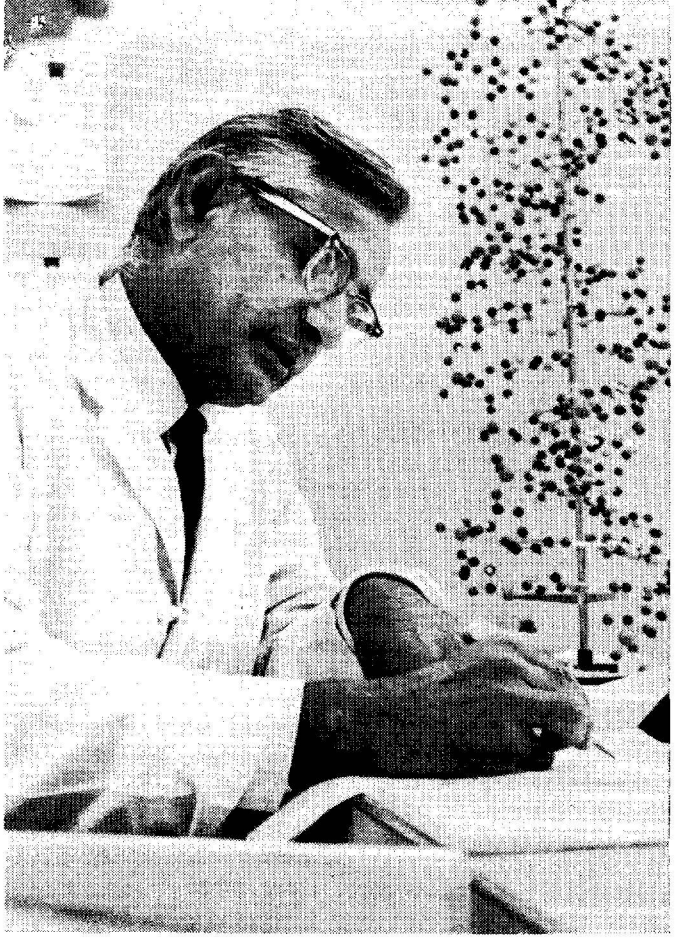

Dr. Khorana achieved the first total synthesis of a gene in his Wisconsin laboratory. Behind him is a partial model of the gene he made

SCIENTISTS SYNTHESIZE A GENE . . .

Dr. H. Gobind Khorana, in an elegant swan song to his 10-year career at the University of Wisconsin's Institute for enzyme research, has synthesized a gene from nucleotides, the simple chemical building blocks that when strung together make up the hereditary machinery of life.

Dr. Khorana's team is the first to put together an entire "informational strand" or gene by synthesis. Previous work—notably that of Dr. Sol Spiegelman, then of the University of Illinois, with viral RNA and Nobel Laureate Arthur Kornberg of Stanford with DNA—began with an informational strand and used a purified polymerase to replicate this strand. Dr. Khorana has yet to demonstrate that a totally synthetic gene will be able to function within a cell.

Dr. Khorana—who received the Nobel Prize in 1968 for his work in clarifying the genetic code—used the gene for alanine transfer RNA (t-RNA) from yeast as a model to produce his synthetic gene.

The gene made by Dr. Khorana and his group is a molecule of DNA (deoxyribonucleic acid) made of two strands. Each strand is composed of four nucleotides; these consist of four bases: adenine (A), thymine (T), guanine (G), and cytosine (C). These bases are linked to a sugar and a phosphoric acid molecule. The two strands of the gene are wound in a helix with the A's of one strand always opposite the T's of the other, and the G's opposite the C's.

Dr. Khorana started with the four nucleotides that can be chemically synthesized with ease. He joined the nucleotides into a number of short single-stranded segments with the nucleotides in proper sequence, then later enzymically joined these fragments into the complete double-stranded 77-nucleotide gene.

Now that the synthesis has been accomplished, there remains the ultimate test of introducing the synthetic gene into a living cell which lacks it, and checking to see if the cell is transformed into a normal cell. Other more immediate tests for biological activity can be carried out and are now underway. Once such would involve learning how to copy the gene in a test tube using DNA polymerase. The next task might be to produce t-RNA using the synthetic gene. There is also the matter of learning whether the gene, if it will function at all in a living cell, will produce RNA in the right quantities. This step implies a better understanding of the initiation and termination signals for RNA polymerase.

The Wisconsin University scientist's group is also working on the synthesis of a second gene, tyrosine-supressor t-RNA, found in the bacteria *Escherichia coli*. This synthesis should be complete in a few months, says Dr. Khorana, and, as mutants lacking this gene are already known and are available, testing its biological activity should be relatively simple.

Spiegelman, now director of the institute of cancer research at Columbia University, believes that Dr. Khorana's work represents something more on the order of a technical achievement than a real breakthrough. Though Dr. Khorana claims a complete synthesis, Dr. Spiegelman notes that he used enzymic, not strictly chemical, means and relied on a preexisting "template" in aligning the four bases into the proper sequence. Dr. Spiegelman implies that such a method is something less than creating a living system out of whole cloth.

In addition, Dr. Spiegelman says that although the four bases used to produce the gene may be properly aligned, they must still be modified to produce t-RNA. Thus inosine, dihydrouridine, and pseudouridine—elements of yeast alanine t-RNA—must be produced by enzymic modification of A-T base pairs in the gene DNA.

Indeed, Dr. Khorana assumes that these modifications occur after transcription of the DNA gene containing the four paired bases. But such an assumption has not yet been proved.

Dr. Khorana announced his results at a small meeting of biochemists in Madison, Wis., in recognition, he said, "of the support and encouragement" he has received from the university over his 10-year career there. His announcement was made without fanfare and, since he immediately ducked from public view, the press has had little chance to ascertain any details concerning his team's experimental procedures or his views concerning the magnitude of his achievement. The first full disclosure of Dr. Khorana's work is scheduled for publication in *Nature*. He will also speak on his work before an international symposium at Riga, U.S.S.R., sponsored by that nation's Academy of Sciences.

In the fall, Dr. Khorana will move to Massachusetts Institute of Technology, taking his nine-man international research team with him.