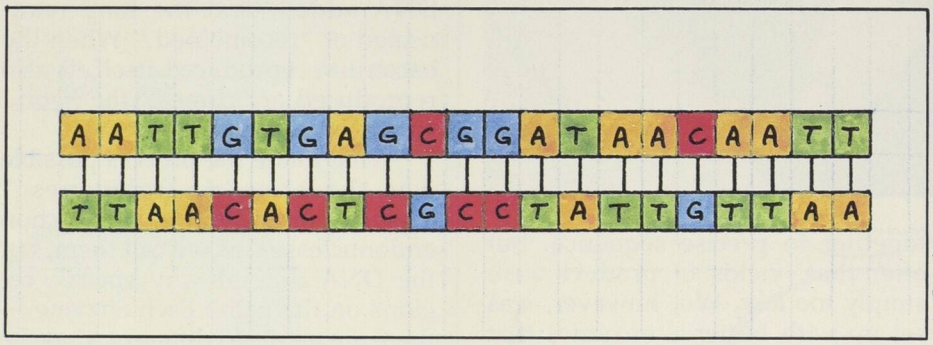
difficulties it posed in trying to isolate the lengthening chain from the reacting nucleotides. These hooks give a molecule what is called an "ionic" character, and as all chemists know, this makes it soluble in water, and not in "organic" or fat-like solvents. As such, the materials could not be purified using the battery of sophisticated techniques available to organic chemists at the time.

Aware of these drawbacks, Saran Narang began to experiment with ways of modifying the method. The hooks, he knew, differed in their capacity to grip other hooks and to hold the masking cork stoppers, depending on the nature of the chemical environment around them. Over the years, Narang had acquired a sure sense of how to manipulate these environments, how to stick different masking corks on hooks, and how to gently tease corks off certain hooks without disturbing others. His idea was to mask the second hook, making the molecule more soluble in organic solvents, and then work out the complicated sequence of chemical environments that would allow him to harvest the building nucleotide chain rapidly, without losing too much in the purification procedures. For Narang and his colleagues, the going was slow and often depressing, given that the labs they were competing with in the United States and Europe had teams of researchers in the same area. Eventually, however, and Narang recalls that it happened during the Christmas holidays of 1972, they worked out the kinks in their new method, which later came to be known as the "modified triester approach". Now, Narang's lab no longer had to worry about water solubility, problems of purification, low yields, or long delays. Their essentially neutral (rather than ionic) molecules could be handled much faster and the yields of product were much higher. Explains Narang: "It was simpler, more practical, and a lot more appropriate to the task of building the genes of living systems, which, as we know, normally stretch to many hundreds of nucleotides in length."



John Bianchi

The operator gene. This 21-base length of 'duplex' DNA (i.e. both strands) was the first artificial gene shown to function in the manner of the natural product. The operator does not hold the code for a sequence of amino acids; rather, it participates in the control of gene expression in the bacterium E. coli. Saran Narang and Drs. Keichi Itakura and Nobuya Katagiri built the gene in 1975.

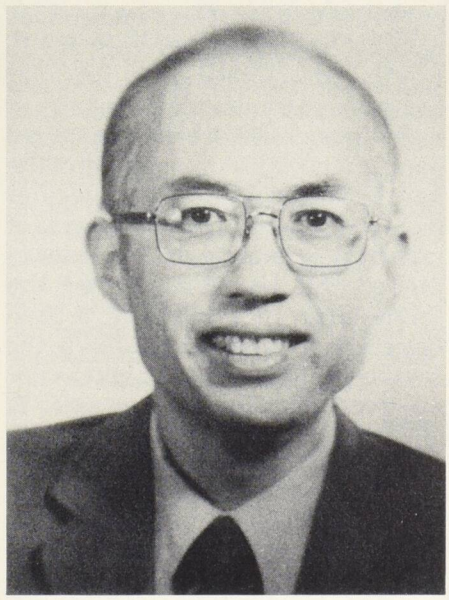
But, what to try first? To begin, Narang not only wanted to build a gene, but he wanted to verify his new methodology as well. Such a dual purpose called for a gene that was both small — and not many were — and could be checked for what is called "biological activity," that it actually works like a natural gene. Narang's chance came when Dr. Walter Gilbert of Harvard University (the 1980 winner of the Nobel Prize) worked out the nucleotide sequence of a very special type of gene in the bacterium *E. coli* called an "operator" gene.

Explains Narang: "We now think that most bacterial genes are controlled by upstream 'operator' regions, which have proteins stuck to them when the genes are 'turned off'; these are called, appropriately, 'repressor' proteins. Gilbert's operator controlled the gene for an enzyme that breaks down the sugar lactose. It is this sugar, when present in the bacterium's environment, that lifts the repressor off the operator, leading to production of the enzyme that ultimately breaks it down for further digestion. When all the sugar is gone, the repressor returns and enzyme production shuts down. It's a fairly simple feedback control system."

Narang indicates a drawing on the wall. A string of base letters, 21 in all, stretch across the paper. Under the string marches another matching letter line, with adenosine always dutifully lined up above or below thymidine, and cytosine with guanosine. It is Gilbert's operator gene.

"We built it in less than four months," he says. "Much faster than the older method, which would have taken at least two years, and we got a lot more product at the end. You'll notice that we needed to build both complementary strands — the way the gene exists in nature. We call such a natural strand 'duplex DNA'."

The Canadian gene was sent to Dr. Ray Wu at Cornell University in Ithaca, New York, who showed clearly that the synthetic gene bound exclusively to the repressor protein, and that the union was disrupted by the sugar lactose. It was, as Narang remembers with pleasure, the first man-made gene that was shown to have the same biological activity as its natural counterpart. It acted like the real thing.



Cornell University

Dr. Ray Wu of Cornell University in Ithaca, New York. The vital biological counterpart to NRC's synthetic chemistry.