nucleic acid chemistry. Better than most others in the field, they knew how to synthesize small sequences of DNA's base letters, connect them into larger molecules with enzymes, and check the accuracy of what they had made.

With the code broken, the next obvious step in the field, particularly for Saran Narang who had done much of the DNA synthetic work for Khorana, was to build an actual gene. When he arrived in Ottawa in 1966, he set himself a goal — to synthesize a large, important gene like insulin using nucleotides from the laboratory shelf as raw materials. Elsewhere, microbiologists working with bacteria and viruses were taking the first steps towards providing Narang and others who dreamed of building genes with an essential downstream vehicle — the methods of recombinant DNA, or genetic engineering.

But, there were obstacles, not the least of which was the dearth of known gene sequences to copy. More serious, however, was the grindingly slow pace of the chemistry. Khorana, who would eventually build the first long synthetic gene — upwards of 200 base letters long — expended the equivalent of 20 person-years on the task. Though the feat was widely acclaimed, it was compared to a once-only lunar landing, with little hope that it would become a routine procedure. Khorana's method, called the "diester approach," was simply too slow and it gave very small amounts of final product.

The gene letters are not, after all, strung together in one single chemical step; rather, they must be assembled pyramid-like, attaching the base letters one after another onto the lengthening DNA molecule. But each time a nucleotide is coupled or "condensed" to the string, the product must be elaborately purified, and verified to be what the chemist intended it to be. A lot of material is used up in purifying the lengthening molecule, and after relatively few additions, the amount of product is greatly diminished.

To appreciate the problems of working with these nucleotides, think of them as structures containing a number of different hooks. These hooks are "chemically active" groups, and gene builders want only one of them to undergo the coupling reaction. If they are thrown into a solution unchanged, then the hooks can link up the nucleotides in any number of ways. To avoid this, Narang and others "mask" or make chemically inert all groups except the one they want to remain active. Think of it as putting cork stoppers on all the hooks except one. Once the chain has been built to the chemist's specifications, the masking corks are removed to yield the nucleic acid chain as it would occur in the cell.

In Khorana's technique, there were actually two hooks still free when he linked up nucleotides; once one had formed a link with another nucleotide, however, the remaining hook wasn't nearly as apt to form a link as well. The real problem posed by the presence of this second hook, was in the way it affected the rates of the chemical reactions, and in the

The double edge of DNA

During the mid-1970's, a socio-political storm blew up around the fledgling science of genetic engineering. The controversy arose not from outside the field but from within, from the ranks of the scientists themselves.

For many, recombinant DNA technology heralded the beginnings of a new era, promising an understanding of life and its control mechanisms that would have far-reaching consequences for medicine and industry. For others, however, its evoked scenarios of a future fraught with danger. The issue, which probably ranks as one of the most important social developments in the history of molecular biology, began in 1974 with what seemed like a fairly innocuous experimental idea by Stanford's Dr. Paul Berg. Berg's plan was to use the new techniques to insert genes from a monkey virus called SV40 into *E. coli*, using a virus rather than a plasmid as the 'vector' for getting the DNA into the bacterium. But, as some appalled microbiologists realized, SV40 caused lab-grown human cells to become cancerous, and *E. coli*, the workhorse of molecular biology, was completely at home in the human intestinal tract. There was a fear of loosing a truly dangerous bug onto the human population, one that could conceivably confer cancer on its host.

However, the problem was even more serious than this. Scientists could, after all, simply agree not to do such risky recombinations as SV40 — *E. coli*. But recombination experiments in general were far from exact. When microbiologists transferred genes from different organisms into bacteria, there was a possibility of inadvertantly splicing an unlooked-for gene into the bug that would make it dangerous to humans.

The protests resulted in a group of scientists, led by Berg, asking for a voluntary moratorium on gene-splicing experiments until the dangers could be properly assessed. Finally, it spilled over into the public domain, leading to guidelines which called for such safeguards as special containment facilities for the work, the use of 'crippled' *E. coli* test bacteria which could not survive outside the lab, and an outright ban on certain experiments with disease organisms.

Though time has shown that much of the concern was unfounded, and that many of the feared mixings of gene material take place naturally, research in the field is still infused with the earlier caution.