There are no secrets, but developing countries must now appropriate the new techniques if they are to benefit.

**BIOTECHNOLOGY: PROMISE... AND PERIL**

JEAN-MARC FLEURY AND ROWAN SHIRKIE

A new technological revolution has begun. Newly evolved techniques for the genetic manipulation of simple organisms like bacteria, yeasts, and fungi have enabled scientists to change the functioning of living things to make them more useful to humans. The power of the technique lies in the recently acquired ability to alter the "genetic blueprint" of DNA. DNA (deoxyribonucleic acid) is the complex molecule in which all the information required for the creation and operation of each cell in an organism is coded in units called genes. By selecting genes responsible for a particular product in one organism and recombining them in the DNA of another, biochemists can create a "bug" specifically to manufacture the desired product.

Biotechnology is simple biochemistry for which all countries have the facilities, says Dr Saran Narang, molecular biologist at the National Research Council of Canada, and one of the world's leading researchers in the field. "It's not like nuclear technology where you need complex hardware like a reactor, and uranium from foreign countries. It is simple biochemistry. Every country has the facilities; all it needs is the training. Our university undergraduates will be using the techniques next year." But in order to take advantage of the genetic technology, he says, developing countries must first be alerted to its potential and begin to acquire the critical skills that will be needed in the future. The achievements of basic research must still be translated into useful products, and the move from the laboratory to successful application is by no means as simple (see box, page 7). "That is where the work must now begin," says Dr Narang.

In fact, developing countries already have a tradition of biotechnology that reaches into households and industry. The controlled action of microorganisms...
to preserve or process food becomes more familiar when the products are mentioned: bread, cheeses, beer and wine, yoghurt, and pickled vegetables. Fermented meat-substitute foods such as tempeh and tofu are widely consumed in Asia, and soy sauce spiced dishes around the world. They are the result of refined microbial processes.

Japan has built on its traditional fermentation industry to produce the industrial chemicals and enzymes, vitamins, antibiotics, and alcohols that are now responsible for six percent of its income. Intensifying the natural decomposition of organic material—waste treatment—is the world's largest microbiological industry.

All of the conventional microbial processes now in use stand to be improved and made more efficient by biotechnology. The near future will also see the development of many novel applications.

Much of health science concerns itself with the harmful or healing properties of microbes. Living in perpetual competition with each other, microbes defend themselves by secreting antibiotics...which humans extract on an industrial scale to protect themselves, in turn, against bacterial infections. The pharmaceutical industry is also developing bacterial enzymes to dissolve blood clots, clean burn tissue, or facilitate digestion.

But with the progress of genetic engineering, pharmaceutical biotechnology borders on the spectacular. In the space of two years, geneticists have taken an innocuous bacterium from our intestinal flora, Escherichia coli, and made a "microfactory" producing medications worth billions of dollars. E. coli are now made to produce insulin, growth hormones (for treating dwarfism), beta-endorphin (a substance secreted by the brain to reduce pain), and interferon (first anti-viral medicine, which may prove effective in fighting cancer). Genetic engineering also opens the door to completely unprecedented vaccines, including one against the most widespread of diseases, malaria.

AN ANTIMALARIAL VACCINE

One billion people are exposed to the malaria parasite and, rather than improving, the situation is getting worse. The mosquito that transmits the disease is developing an increased resistance to insecticides, and the parasite itself has grown more tolerant of drugs. An antimalarial vaccine would be virtually the only hope in many regions where the infection appears to be permanently entrenched.

Efforts to develop a malaria vaccine have failed because the malaria parasite undergoes several different transformations in the human host. Up to now, it has been impossible to identify a specific substance from the parasite that could be used in a vaccine. But recently, one of the new biotechnology techniques has permitted the identification of a molecule from the parasite's early stage that successfully stimulated the immune system.

The chemical synthesis of this large molecule, which would be required in large quantities for a vaccine, is impractical. Genes responsible for the molecule production could, however, be inserted in E. coli. And according to Ruth Nussenzweig, of the New York University Medical Centre team researching this approach, there is no solution other than engineered bacteria for the large-scale production of the new malaria vaccine.

While waiting for the malaria vaccine breakthrough—which may come about sooner than expected—genetic experts are already busy producing other important vaccines. British, French, and American teams have introduced genes from the hepatitis B strain into bacteria, an important step in the development of a vaccine against the most pernicious form of hepatitis. In Montreal, researchers at the Institut Armand-Frappier are trying to perfect vaccines against rubella (German measles) and poliomyelitis, having already created a new vaccine against influenza containing antigens that will be manufactured in recombinant bacteria.

Still in the field of vaccination, in western Canada at the University of Saskatchewan, George Khachatourians, working on a vaccine against cholera, using "minicells"—another new biotechnology. Khachatourians creates the minicells by selecting a mutant strain of E. coli, into which he introduces genes from the pathogenic agent. When the mutant divides, instead of producing the usual two identical cells, it forms a large and a small cell. The pathogen antigens are carried on the surface of the small cell or minicell, but the cell itself has no internal genetic material, so it cannot reproduce. The risk of infection is thus eliminated, although the production of antibodies is still highly stimulated. These minicells augur well for the development of a more effective vaccine against cholera.

BIOMASS FUELS

Along with health, one of the most pressing contemporary concerns is energy. Biotechnology then becomes vital, too, as alcohol fuels from organic sources rapidly gain acceptance as an economical alternative to petroleum. Alcohol fuels can be produced from sugar or starch crops using yeasts to ferment simple sugars to ethanol. Using largely conventional techniques, Brazil aims to become self-sufficient in automotive fuel by 1982, by breeding alcohol from sugarcane. Advanced techniques now appear to bring a similar measure of independence within reach of many countries.

Sugar crops like cane and beet need only to be pressed and mixed with water to yield the fermentable sugar unit for alcohol distillation. But the sugar units are linked in long branched chains in starch crops such as corn and cassava. High process heat and expensive industrial enzymes, or an acid solution, must first be used to liberate the sugar before yeasts can feed on them. This multiple-stage processing raises costs and, by most analysts, makes fuel production from starch crops uneconomical unless subsidized against petroleum.

If the work of biochemists like Dr Illimar Altosaar of the University of Ottawa, Canada, is successful, the bacterial genes for amylase—the enzyme responsible for converting starch to sugar—may be transferred to yeast. Ethanol production then becomes significantly simpler and cheaper. Other research in Europe concentrates on developing a "superbug" 40 times more efficient than present microorganisms for use in the Brazilian ethanol program. The approach attempts to improve the amylase enzyme activity, and increase the capability of selected bacteria to grow at high heat. The superbug will be an efficient organism that operates at the evaporation point of ethanol (70°C), skipping yet another conventional process, the distillation to purify and concentrate ethanol. Production becomes one smooth, simple, continuous operation involving a minimum of energy and hardware.

Perhaps even more potentially useful is work on the improvement of fermentation processes for cellulose materials such as crop wastes and wood. Cellulose is the main component of plant biomass, the skeleton of cell walls in stems and leaves. As such it is strongly resistant to degradation, and the chemical bonds holding cellulose molecules are much stronger than those of starch.

Conversion is possible only by a combination of high heat and pressure, together with acid. Efficiencies are poor. Cellulose represents only about 50 percent of the biomass; the rest, equal parts of hemicellulose and lignin, is not used in normal distillation. Engineered cellulase enzymes that
THE GENETIC MECHANISM

All living organisms are built around large molecules that have been called "the ultimate parasites", but that most scientists name DNA, for deoxyribonucleic acid. The information required for the creation and operation of every cell in an organism is encoded in DNA units that are called genes. A virus has 10 to 50 genes, a bacterium has several thousand, and a human cell has tens, if not hundreds, of thousands. Trying to find and use a specific gene in a complex organism would be like looking for one particular book in a library filled with thousands of volumes without titles or labels. If it were not for the remarkable shortcuts of genetic engineering.

Briefly, genetic engineering involves three main operations: cutting DNA into its constituent genes using molecular shears known as restriction enzymes; reassembling the genes in different combinations (called recombination); and introducing the recombinants into living cells.

Recombination generally links a gene controlling the manufacture of a protein to the genetic material in a bacterium, which then adopts the foreign gene as its own and begins producing the new protein. In one type of genetic manipulation, bacteria are put into a veritable "gene soup" known to contain some of the desired genes. A number of bacteria will adopt that gene, thereby becoming recombinant bacteria, but they still have to be identified and separated out of the mix. Sometimes the substance synthesized by the new gene can be used in the search.

For example, bacteria have been exposed to genes from human cells in a search for those containing the code for the synthesis of interferon — an antiviral substance. The successful recombinant bacteria can be identified by exposing all of the bacteria to viruses. Only the bacteria that have adopted the gene for interferon synthesis will survive the viral attack. Multiplying copies of the recombinant cells - cloning — will make it easier to produce this very rare substance.

The new techniques will also apply to the genetic improvement of food crops as research expands to more complex lifeforms. But even now, engineered bacteria have a place in efforts to boost food crop yields.

Air is 80 percent nitrogen, yet it is lack of this particular element in soils that most often limits food production. Plants cannot use elemental nitrogen directly. It must be fixed, or combined with other elements such as oxygen, carbon, and hydrogen in a form that plants can assimilate.

The fertilizer potential of nitrogen-fixing bacteria that live on the roots of most legume plants has been improved and exploited in recent years. Biotechnological research is attempting to isolate the genes responsible for nitrogen fixation in these bacteria and adapt them to major cereals like wheat to produce plants that are nearly nitrogen-self-sufficient.

For developing countries, biotechnology may bring unique short-term problems. Most of the research now under way in developed countries aims at the total synthesis of organic materials. Where does that leave the developing countries, whose economic mainstays are those very organic or raw materials?

Sugar is an excellent example: after petroleum, coffee, copper, and timber, it is the fifth most important export commodity in the Third World. Market fluctuations that depress and inflate sugar prices in boom-bust cycles have damaging effects on developing country economies. Current high prices, together with restrictions on artificial production, perform the necessary conversion will greatly improve the process. But, just as with starch fermentation, researchers are attempting to develop a bug that will use cellulose directly, converting it to ethanol in one step, while also making better use of the other materials present in biomass. Thus, both food and energy can be accommodated within the same agricultural system, instead of making disastrous competing demands on it as some have feared.
in a process that was intended to be simple, hardy, and adapted to a rural environment.

The adjustments to the production process needed to accommodate C. eichhorniae and eliminate the aerosol dust may make it too complex and fragile. The fungus itself could be further improved through classical genetic techniques. If so, the researchers would also like to add the capacity to use sugar and cellulose, broadening the range of alternative raw materials for protein production.

The microbial protein project serves to demonstrate just how many things intervene between biotechnology and its application in developing countries. Its success lies as much in the knowledge gained of the problems as in the resolution of many of them.

ROWAN SHIRKIE