J. Natn. Sci. Coun. Sri Lanka 1994 22 (Suppl. A) : S1-S5

THE SCOPE OF MODERN BIOTECHNOLOGY

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INTRODUCTION

The use of other living organisms for industrial production geared to improving man's quality of life may be termed *Biotechnology*.[1] Taken in this broad sense, the practise of Biotechnology goes back a long way. Men in the Middle East are recorded to have transformed wild varieties of wheat into the cultivated varieties, through selection of desired traits, in 9000 B.C. Rice cultivation was reported in South-East Asia by 4500 B.C. Domesticated varieties of sheep and goats were known by 7500 B.C. and cattle a few millennia later. The cultivation of cotton for producing cloth was recorded in the Indus Valley by 3000 B.C.

Unravelling the structure of deoxyribonucleic acid (DNA) in the early 1950s was a landmark in both Chemistry and Biology and gave birth to a new science - Molecular Biology. Together with the subsequent discovery of restriction enzymes i.e. enzymes that cleave DNA at particular sequences of nucleotides, these became some of the critical scientific discoveries that led to the development of the technology of gene cloning. Modern biotechnology makes use of numerous such advances in basic or fundamental science to exploit the potential of other living organisms for human benefit. The European Federation of Biotechnology in 1981 adopted the following definition: Biotechnology is the integrated use of biochemistry, microbiology and chemical engineering in order to achieve the technological application of the capacities of microbes and cultured cells.

Biotechnology may be broadly classified into three areas *viz.* Biotechnology in relation to Health, Agriculture and Industries.

Biotechnology in Relation to Human Health

Some of the applications of biotechnology for improving human health in countries such as Sri Lanka are:

(i) Development of vaccines

Infections are a major cause of human illness and death in tropical countries. Immunization remains the principal method of preventing many viral and bacterial infectious diseases. A notable success of the vaccination approach has been the eradication of smallpox. Synthetic vaccines based on defined molecules of the pathogens afford many advantages over the more conventional vaccines based on attenuated or dead pathogens. Indeed in the case of a malaria vaccine, the use of conventional vaccines is not possible because *Plasmodium falciparum* is cultured in

human blood and blood - derived vaccines may transmit pathogens such as the human immunodeficiency (AIDS) and hepatitis viruses. Whole proteins produced by recombinant DNA technology and chemically synthesized peptides are the more common forms of synthetic vaccines. For example a yeast derived recombinant vaccine against Hepatitis B, based on the major viral surface protein, is already widely used.

(ii) Immunodiagnostics

The diagnosis of disease often depends on serological typing of pathogens. Polyclonal antibodies present in most typing sera often lack adequate specificity in this regard. The advent of monoclonal antibodies has revolutionized immunodiagnostics. Because of their unique specificity, they can be useful in detecting minor variants of a pathogen eg. dengue virus subtypes.

(iii) DNA probes for disease diagnosis

The enzyme DNA polymerase had the distinction of being described as the molecule of the year in the journal *Science* in 1989. A heat stable form of the enzyme can be used in a process known as the Polymerase Chain Reaction (PCR) to generate millions of copies of a given sequence from a molecule of DNA. The PCR reaction has given rise to many applications and a major use is in the diagnosis of disease. Where the DNA sequence of a part of the pathogen genome is known, the PCR reaction can be used to amplify the sequence over a millionfold, and the amplified DNA can then be detected with a radioactively or enzymatically labelled complementary DNA or DNA probe. The use of DNA probes provide a very sensitive and specific assay for disease causing organisms that may be difficult to detect and identify otherwise.

(iv) Cancer immunotherapy

Monoclonal antibodies against tumour specific antigens that are also covalently linked to a toxin molecule have been termed *magic bullets* for ridding the body of cancer.

(v) Cancer imaging

Specific monoclonal antibodies that are tagged with radioactive or heavy atoms yield information on the location and spread of tumours.

(vi) Tissue typing

Before transplantation, it is necessary to match the donor and recipient tissues for histocompatibility antigens. Similarly, blood groups need to determined before transfusion. Monoclonal antibodies, because of their great specificity are very valuable in this task.

(vii) DNA fingerprinting in forensic medicine

The pattern of restriction enzyme digested DNA after separation by size on an agarose gel and reacted with specific DNA probes is characteristic of an individual. This technique can be used to trace the origin of human tissue samples such as blood, hair follicles and semen. Forensic evidence of this type is now accepted in the law courts of many countries.

(viii) DNA analysis in determining genetic pre-disposition to inherited diseases

Considerable effort is being directed towards identifying the genes responsible for many inherited disease. Genetically transmitted diseases include many types of cancer, haemoglobinopathies, cystic fibrosis, muscular dystrophy etc. While many of the responsible genes have been identified, it is possible to associate several unidentified genes with specific changes in restriction enzyme digest patterns (restriction fragment length polymorphism or RFLP). The RFLP patterns can then be used in diagnosis.

(ix) Production of physiologically active proteins for medicinal use

Many proteins that are pharmacologically active or useful have the potential for production by recombinant DNA techniques in commercially viable quantities. Tissue plasminogen activator and various cytokines are already produced in this way.

(x) Gene therapy

Gene therapy ie. the correction of genetic defects in man by the introduction of new genes at the somatic stage, is the ultimate dream of molecular biologists. Tumour infiltrating lymphocytes from a patient terminally ill with melanoma are used to deliver various cytokines with anti-tumour activity. Experiments are underway to correct deficiencies in blood clotting, cystic fibrosis, adenosine deaminase and lysosomal storage diseases.

Biotechnology in Relation to Agriculture and Veterinary Medicine

Many of the applications of Biotechnology that have been described for human medicine are also of value in veterinary medicine eg. diagnosis of infections, vaccines, etc. However, a major application of genetic engineering in regard to animals is in stock improvement. The production of transgenic animals is now a relatively trivial procedure and involves the introduction of embryo cells from one strain into the blastocyst of another *in vitro* followed by implantation into a pseudo-pregnant female. Genetic engineering will go hand in hand with traditional breeding procedures for stock improvement in the future. Indeed genetically engineered animals producing recombinant proteins in milk are considered to be a ready source of proteins useful in human medicine.

Agriculture related Biotechnology[2] is about one hundred times bigger than human health related Biotechnology in terms of financial turnover. Much of the activity in Plant Biotechnology involves the use of tissue culture for the propagation of elite genotypes and the use of genetic engineering to produce plants of the desired phenotype.

Tissue based micro-propagation may be the only way of obtaining large numbers of plants of a specific type, free from viruses and other pathogens. Another application of tissue culture lies in the effort to preserve germplasm.

As an example of genetic engineering we may consider the production of herbicide and pest resistant cereal plants. Genetic engineering in plants has involved the cloning of the gene of interest in an *E. coli - Agrobacterium tumefaciens* shuttle vector and then recombination into the Ti plasmid of *A. tumefaciens* which is in turn used to infect plant tissue and transfer the gene of interest into the plant genome by recombination. Electroporation and other techniques are now considered superior for introducing foreign genes into plants. In addition to improving plant characteristics, it has been possible to genetically engineer common plants to produce recombinant proteins of medicinal importance in large amounts.

Other major applications of biotechnology in agriculture include:

(i) Identification of plant pests (especially in seeds) using DNA probes and monoclonal antibodies

(ii) Production of improved nitrogen fixing symbionts.

(iii) Use of RFLP and RAPD analysis to identify useful genes in the plant genome. This will greatly simplify the process of classical plant breeding.

(iv) The production of genetically engineered microbes for the biological control of insect pests. The best example of this approach is the use of the endotoxin produced by *Bacillus thuringiensis*.

Industrial Biotechnolgy

(i) The production of ethanol by yeast induced fermentation is an age old biotechnological process. However this has now been extended to the production of other industrially important chemicals including acetic acid, amino acids, fructose and antibiotics. Enzymatic processes are being developed for the economical conversion of woody material and other agricultural by-products into useful substances such as sugars. Plant cells in tissue culture are also a potential source of medicinal chemicals, flavours and vitamins.

(ii) Enzymes find uses as probes (biosensors) to detect concentrations of chemicals in blood and industrial manufacturing plants.

(iii) The use of micro-organisms for the treatment of wastes.

(iv) The use of microbes in mineral extraction.

(v) Antibodies made to transition state analogues of a chemical reaction are able to function as catalysts in a variety of chemical reactions, some of considerable industrial importance.

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