BIOTECHNOLOGY:

THE CANADIAN EXPERIENCE

Canada

External Affairs and
International Trade Canada

Plant explants in the culture medium (overall plan).
(Agriforest Technologies Ltd.)

Cover photo:

The T cells that bond with monoclonal antibodies light up. The percentage of fluorescent cells indicates the power of the antibody tested.
(Ortho Pharmaceutical (Canada) Ltd.)

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Contents


The purpose of this series is to inform readers of current trends in Canadian science and technology.

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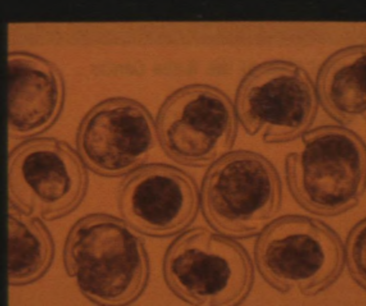



Introduction

Human beings have long used micro-organisms to produce the things they need. Since people first began to make beer, bread, wine or cheese, they have been using biotechnology, even though these traditional technologies were not known as such.

However, only the most recent discoveries of biology and genetics, and the areas to which they have been quickly applied, have opened the way for modern biotechnology. It took about 15 years for "selected" or "manipulated" micro-organisms to become (or at least hint at becoming) industrial giants. These are now the stars in the biotechnological firmament.

Biotechnology has become the nucleus of a true technological revolution that is blazing new trails in the fight against disease, allowing traditional sectors such as the agri-food and forest industries to modernize and increase their productivity, providing new weapons for the fight to protect the environment and forests, and making it possible to develop new industries, such as bioelectronics, and to create new products.

Already, biotechnology is responsible for introducing new synthetic substances and producing existing products at a lower cost, and for developing more effective, inexpensive and less polluting processes. Here is proof of the dynamism and know-how of Canadian biotechnology.

Canada is carving out an enviable position for itself in an extremely competitive biotechnological and bioindustrial field and is in the forefront of advanced research in biology, genetics and biotechnology-based business endeavours.

The use of the term "biotechnology" is a recent phenomenon, originating with an epoch-making discovery in the history of the biological sciences. In 1973, researchers in Stanford, California, succeeded in carrying out an experiment of vital importance. After cutting DNA (deoxyribonucleic acid) fragments that carried a particular gene from a cell, they were able to transfer that gene to another cell, thus achieving the very first gene transplant.

Since that time, genes have become concrete entities that can be manipulated at will, and this has led to the rise of the "age of genetics." It is now possible to manipulate the genetic coding (contained in the DNA) of all living organisms, from bacteria to human beings. Because of genetic engineering, it is even possible to reprogram micro-organisms in order to make them produce certain desired substances continuously.

However, the biotechnologies used by those working in this field are not restricted to genetic engineering. They also include cellular fusion, which is the basis for the production of hybridomas for diagnostic or therapeutic purposes. In agriculture and forestry, they consist mainly of cell and tissue cultures. Enzymatic and fermentation engineering techniques also play an important role, especially in the food and pharmaceutical industries, because they make it possible to domesticate microbes effectively and use them to produce various substances that meet people's needs.

Aerial view of the Balco Canfor greenhouses.
(Balco Canfor Reforestation Centre Ltd.)

Equipment used in the waste-water purification process (waste produced by cheese production and washing water).
(Coopérative agro-alimentaire Agropur)

In the last few years, more discoveries have been made and new applications have been developed. At present, Canadian biotechnology researchers work mainly in such key sectors as health, the agri-food and forestry industries, the control of environmental pollution and mining.

The National Research Council (NRCC), which is Canada's national laboratory, fulfils its mandate to promote the development of expertise in biotechnology and help industry carry out commercially promising research activities through the National Biotechnology Program. In order to do this, the NRCC takes advantage of its high-level network of laboratories that includes the Biotechnology Research Institute in Montreal, the Plant Biotechnology Institute in Saskatoon and the Biological Sciences Branch in Ottawa.

This network is continually growing and encompasses a large number of Canadian universities and private-sector companies seriously committed to biotechnology. From coast to coast numerous Canadian companies that are deeply involved in research and development (R&D) efforts in biotechnology are beginning to thrive as a result.

It is expected that the biotechnology market will be worth some 60 billion dollars by the year 2000.[1] Though not a world leader, Canada is now starting to claim a share of this promising market. Relying on creative individuals, as well as sophisticated equipment and cutting-edge expertise, Canada aims to capture a position in the forefront of research in biotechnology, and to take advantage of the innumerable possibilities offered by this new and powerful technology.

1. Roger Miller, *The Strategic Management of Biotechnology R&D for the Successful Industrialization of Biotechnology.* Second Industrial Biotechnology Conference, NRCC, 4 and 5 December 1986.

The Health Field: Beginning to Realize the Potential

The health field is one of the most important areas of application for biotechnology, and the products of this technology are now starting to be introduced on the market. These include alpha interferon, the human growth hormone, human insulin, a vaccine against hepatitis B and a monoclonal antibody that can be used to prevent the rejection of organ transplants (OKT 3).

Canada has always been particularly active in this field: Canadian researchers discovered insulin and were the first to clone human proinsulin.

According to the strategic plan published in 1984 by the Biotechnology Research Institute, the market for pharmaceutical, diagnostic and biological products in Canada will reach a commercial value of over two billion dollars in 1995.

Monoclonal antibodies: Diagnostic and therapeutic tools

Diagnostic tests for the detection of pregnancy, the monitoring of diabetes, the detection of some sexually transmitted diseases (STDs), the detection of cancer of the colon and of cancer of the breast and lungs in particular, and the diagnosis of allergies and viral hepatitis have undergone considerable expansion. Such rapid development is based on a fundamental discovery: monoclonal antibodies.

Antibodies are naturally produced by blood lymphocytes when foreign substances, or antigens, penetrate the organism. However, these antibodies cannot reproduce indefinitely. In 1975, the English researchers Köhler and Milstein found the solution. For the first time they were able to obtain, from a single mouse cellular strain, an unlimited quantity of antibodies that were all identical and extremely specific. These were the first monoclonal antibodies.

By fusing two different cells, researchers could obtain a "hybrid" cell, known as a hybridoma, which has the genetic characteristics of the two parent cells. In order to produce a specific antibody, that is, one capable of recognizing a very precise substance, all that is necessary is the fusion of a cell that can manufacture this antibody with a cancerous cell that has the capacity to reproduce indefinitely. The hybridoma multiplies by producing genetically identical cells, or clones, and the antibody is thus said to be monoclonal.

Until recently, antibodies were obtained by immunizing an animal and extracting the antibodies from its blood. However, the product always contained impurities. The discovery of monoclonal antibodies has solved this problem. The high specificity and purity of monoclonal antibodies, and the fact that they are relatively easy to obtain, makes them first-line tools for the preparation of "diagnostic kits."

Quadra Logic Technologies Inc. of Vancouver, British Columbia, is involved in the development and marketing of immunological diagnostic products for people and animals. The company has been able to develop diagnostic kits on the basis of monoclonal antibodies for the early detection of leukemia, lung cancer and German measles.

In Edmonton, Alberta, Chembiomed Ltd. was one of the first firms in the world to market a series of reagents, in particular the Syntype typing reagent, for the determination of blood type using monoclonal antibodies.

The Institut Armand-Frappier, located in Laval near Montreal, Quebec, is a leader in marketing diagnostic kits. Specifically, the company has marketed kits for the diagnosis of herpes 1 and 2 and the cytomegalovirus.

Medicorp Inc., a young firm located in Montreal, Quebec, has recently marketed a new product called Quadroma, a bispecific monoclonal antibody produced on the basis of a hybrid hybridoma. Such "bispecificity" allows it to recognize two different molecules, and because of their great specificity and sensitivity, these bispecific antibodies are invaluable tools for immunodiagnostic tests.

The monoclonal antibody technique has also been used for the early detection of cancerous cells, through the radioimmunodiagnostic method. Before being injected into the patients, antibodies that are specific to certain tumour tracers are joined with radioactive isotopes. Subsequently, these antibodies attach themselves to the tumours and can be localized by scintigraphy. Thus, it is possible to detect a certain number of cancers at a very early stage.

At present, researchers are attempting to meld these anticancer antibodies with a substance that can destroy the marked cells. This would make feasible an actual anti-tumour missile, or immunotoxin, capable of destroying cancerous cells without affecting healthy ones. However, this technique is still at the developmental stage.

At the end of 1987, monoclonal antibodies were used for the first time for therapeutic purposes in organ transplant cases. The Ortho Pharmaceutical firm of Don Mills, Ontario, marketed OKT 3, or "Orthoclone," for the treatment of acute rejection of kidney transplants. This special drug makes it possible to neutralize the lymphocyte T cells — those responsible for the organ rejection — in the immune system of the transplant patient. OKT 3 makes it possible to reduce the doses of immunosuppressing drugs, and thus reduce some of the secondary effects that can be disastrous over the long term. To date, more than 30 000 patients worldwide have been treated with the drug.

The hybridoma cells that produce OKT 3 monoclonal antibodies are grown in large quantities in tissue culture flasks. (Ortho Pharmaceutical (Canada) Ltd.)

A new generation of vaccines

Vaccination is one of the most effective tools of modern medicine. Specifically, vaccination has made it possible to eradicate smallpox and control outbreaks of diphtheria and tetanus in countries where prevention is systematic.

However, at present, traditional vaccines have serious limits in terms of effectiveness, safety and cost of production. Without taking into account the fact that five million people throughout the world die each year of diseases for which there are still no vaccines — diseases such as malaria, viral diarrhoea and such STDs as acquired immunodeficiency syndrome (AIDS) — the major disadvantage of vaccines is that they contain whole micro-organisms.

Researchers, therefore, are struggling to develop a new generation of vaccines based on the knowledge acquired in the field of immunology combined with such advanced techniques as genetic engineering. Unlike traditional vaccines, these new vaccines do not contain pathogenic agents that have been killed or inactivated, or any fraction of such agents. They consist solely of elements that provoke an immune response, namely the microbe antigens, and are known as sub-unit vaccines. The key to production of these new vaccines is the identification of antigens that can lead to the secretion of protecting antibodies. However, such identification is the most difficult stage in the process.

Fermenter used in the production of vaccines.
(Connaught Laboratories Ltd.)

In Canada, Connaught Laboratories, a firm engaged in developing, manufacturing and marketing vaccines, has focused on the development of a new type of vaccines created using genetic engineering and peptide synthesis techniques. The company is considered a world leader in the production of human vaccines. In 1987, it sold over 350 million doses of various types.

Connaught Laboratories is also involved in the development of the new so-called biosynthetic vaccines for diseases such as whooping cough, hepatitis B, influenza and AIDS.

The Institut Armand-Frappier is another firm dedicated to vaccine research. It has recently marketed its own vaccine against hepatitis B (Engérix-B), and its researchers are also developing a vaccine against whooping cough.

At the forefront of advanced research, Connaught is also interested in the production of synthetic vaccines, the ultimate in immunization. These vaccines are made from very small fragments of protective proteins that have the power to induce the formation of antibodies. These small molecules, known as peptides, can be easily synthesized in the laboratory, and make possible very powerful and safe vaccines.

In 1988, Connaught Laboratories, in collaboration with Finnish researchers, obtained from a peptide a vaccine against meningitis far more effective than the existing one. Other synthetic vaccines against diphtheria, streptococcal infections and rabies are also being developed.

Protein engineering and peptide synthesis: The last word

The development of recombinant DNA and monoclonal antibody technology has paved the way for the commercial production of new or replacement drugs prepared using proteins and peptides.

Protein engineering makes it possible to act directly at the level of DNA coding to change the protein sequence and create proteins with different properties. For this reason, researchers are seeking molecules that are more stable, active and easy to purify; that are more or less immunogenetic, depending upon the needs; and that have new specificities.

Peptide synthesis is another technique that uses proteins as raw materials. Peptides are, in fact, small fragments of proteins that are naturally found in all living organisms. Numerous companies are already very active in this area of advanced biotechnology.

A company working in the forefront of this sector, Synthetic Peptides Inc. of Edmonton, Alberta, is developing peptides for pharmaceutical and diagnostic applications, as well as for the manufacture of synthetic vaccines. The firm has also developed two computer programs (Surfaceplot and HPLC 1) that facilitate the design of biologically active proteins and peptides.

IAF Biochem International Inc. of Montreal, Quebec, a research-oriented company, is involved in the development and manufacture of products used for the diagnosis and treatment of diseases affecting the immune system. The technology of peptide synthesis represents a significant part of its activities. Biochem uses this technique for the development of new vaccines, immunomodulators and epitope synthesis. As for immunomodulators, the firm uses a peptide synthesis technique, currently being patented, to create stable analogs that have excellent therapeutic potential.

Biochem has also developed a technique known as epitope synthesis, which makes it possible to accurately define antibody bonding points, or epitopes, in order to synthesize the corresponding peptides and modify them so that they correspond to the three-dimensional structure of the original protein. The company is using the technique to develop a new generation of more sensitive and specific diagnostic kits.

Photoactive therapy in the fight against disease, especially cancer

In addition to surgery, chemotherapy and radiotherapy, there is now a fourth alternative in the treatment of cancer: photoactive therapy. This method is based on a photosensitizing agent that forms part of the porphyrin category. These porphyrin molecules, which are hemoglobin derivates, are activated by light.

Quadra Logic Technologies of Vancouver is the world leader in photoactive therapy. The Canadian firm will shortly bring onto the market the first photoactive drug: Photofrin. When used for the treatment of cancer, the drug is injected and then activated by a laser beam focused on the cancerous tumour. When exposed to a light source, Photofrin releases a substance that destroys cancerous cells without attacking the healthy surrounding cells. The company is also considering a technique to put monoclonal antibodies and porphyrins together in order to improve the effectiveness of the treatment.

Aside from cancer treatment, the photoactive drug can be used to purify the blood and eliminate various types of viruses, such as the herpes and AIDS viruses. It has also produced encouraging results in the treatment of arteriosclerosis, psoriasis and various forms of STDs.

Quadra Logic researchers are also working to produce a new generation of more effective porphyrins that do not produce photosensitivity in patients.

A New Era for the Agri-Food Industry

The use of biotechnology in the agri-food industry, one of Canada's largest industries, is likely to lead to diversification and modification of all food products, both those made from agricultural products and those obtained from other sources.

Fermentation: New uses for an ancient craft

More than 4 000 years B.C., a process of fermentation using yeast was already part of daily life. It seems that the Egyptians knew beer and wine yeasts could be used to make bread rise, but they did not understand how to control the process. Bakers and brewers were successful in making their products only by chance.

Only after scholars such as Pasteur and Hansen published results of their discoveries at the end of the last century did fermentation cease to be the result of chance. These researchers demonstrated the action of yeasts in fermentation, and over the past few decades, research has essentially focused upon the improvement of yeast strains and the automatization of the fermentation process.

Lallemand Inc. of Montreal has contributed significantly in changing the face of the "oldest biotechnology" in the world. Lallemand, a major producer of yeasts used in the bakery, winery, distillery and brewery markets, holds 60 per cent of the Canadian market for fresh yeast. For the past 10 years, with the development of some 15 wine yeast strains made for export purposes, Lallemand has also become one of the largest producers of wine yeast in the world.

The company is particularly interested in the development of yeast strains for specific applications. In the bakery field, for example, Lallemand is working to develop yeasts that are resistant to freezing for frozen doughs, yeasts resistant to high osmotic pressures for sweet doughs and yeasts with a high maltase activity for unsweetened doughs.

In the winemaking field, Lallemand has developed a high-performance "Double-Killer" yeast that is derived through precise genetic manipulations and does not contain any bacterial DNA. In addition, the increase in yeast strains has led Lallemand to develop more refined identification techniques.

In other respects, the application of immobilized cell techniques has significantly improved the fermentation process in sparkling wines produced by the champagne method. The immobilization of yeast in micro-bubbles of a natural polymer, such as alginate, for example, makes it possible to seed the culture medium continuously and regularly, while increasing productivity. The use of immobilized cells as biocatalysers is a new and rapidly advancing technique.

Supervisor checking the process of fermentation (fermenter measuring 120 m^3).
(Lallemand Inc.)

Dairy products: Winners in the biotechnology stakes

Dairy products offer enormous market potential for the industrial application of biotechnology, from the development of new processes to the introduction of new products.

In particular, biotechnology will make it possible to adapt cottage industry processes such as cheese-making to production on an industrial scale. This was recently the case in the production of cheddar cheese. With the collaboration of university researchers, the coopérative agro-alimentaire Agropur of Granby, Quebec, Canada's largest cheddar cheese manufacturer, has developed a new process that can reduce the ripening period of old cheddar.

The Agropur development, based on the selection of a special *Lactobacillus* bacteria strain and its use for cheddar cheese production, cuts the length of the ripening period by half. In addition, the new process makes it possible to use pasteurized milk. Agropur's innovation considerably improves the quality of the cheese in terms of both taste and texture and has also allowed Agropur to save several million dollars.

In general, biotechnology has contributed toward great improvements in milk processing techniques to the point where milk can be used for virtually everything. The three main ingredients of milk — lactose, fat and protein — can also be used to manufacture a wide range of products.

Protein is undoubtedly the most useful ingredient in milk. Protein hydrolysis is used to segment the proteins with the help of enzymes, thus providing smaller protein fragments that can be more easily assimilated by the organism. Milk proteins are of high quality and contain special characteristics that make them invaluable to the food, cosmetics and pharmaceutical industries.

Milk proteins are already used in a wide variety of products such as diet foods, frostings, soup mixes, foaming agents, nutritional supplements, cereal foods, etc.

Basin used for cheddar cheese manufacture.
(Coopérative agro-alimentaire Agropur)

Can other food products be far behind?

On a larger scale, the food industry in general continues to reap the benefits of biotechnological developments.

George Weston Limited of Toronto, Ontario, has been active in the food industry for more than 100 years. Through its affiliate, Diversified Research Laboratories Ltd., Weston's has been a leader in research and development in the food industry for more than 30 years. The company has undertaken research in a wide range of areas, including biotechnology, and concentrates particularly on the study of fermentation.

For example, Diversified Research Laboratories Ltd. has developed a yeast-based fermentation process for the production of a cocoa butter substitute. The process is characterized by the use of a single yeast strain that can use inexpensive milk byproducts as a source of food. The substitute product obtained is very similar to the original cocoa butter, but is much less expensive. Moreover, it is entirely compatible with cocoa butter in the preparation of various food products.

Agri-food products can also be used as raw materials for the extraction and purification of enzymes and proteins. STC Laboratories Inc. of Winnipeg, Manitoba, an affiliate of Export Packers Company Ltd., is involved in this field, working with eggs and horseradish. The company extracts and purifies compounds such as "horseradish peroxidase," which is used in tests to measure the cholesterol rate; and avidin, which is prepared from eggs and is used in pregnancy tests. Compounds extracted from agri-food products are used mainly by the pharmaceutical industry.

Bulk cheese being drained (boxes weighing 275 kg each).
(Coopérative agro-alimentaire Agropur)

Biotechnology in the Field . . . and on the Farm

The future of plant production no longer depends upon seed selection and the farmer alone. Today, it also depends upon the contribution of laboratories where biologists and geneticists create greater varieties of new "made-to-order" plants that are healthier, more resistant and more productive — plants that will eventually grow without the use of nitrogen fertilizers.

Growth chamber, culture of plant fragments.
(Microelite Plant Laboratories Inc.)

Micropropagation: A second green revolution

Propagating a rose bush to obtain 300 000 identical bushes or producing 100 000 strawberry plants from a single one in only a few months and in an area measuring only a few cubic metres are miracles that have already been made possible by micropropagation, or the *in vitro* culture of plants.

Cellular or *in vitro* culture, enabling the reproduction of plants from cells rather than seeds, is one of the many revolutionary techniques developed in the field of biotechnology. *In vitro* culture makes it possible to grow new plant varieties that are sometimes impossible to obtain through traditional genetic techniques, and it also makes it possible to propagate healthy, vigorous and disease-free plants in large quantities. Initially used with ornamental or garden market plants (carnations, strawberries, potatoes, etc.), *in vitro* culture is now being used with fruit trees and forest species.

The development of exceptional varieties of plants utilizing *in vitro* culture techniques is of great interest to industry. Indeed, micropropagation is a continually expanding industry in Canada.

Agriforest Technologies Ltd. of Kelowna, British Columbia, is one of the leaders in this field. The company produces over 500 000 plants per year by micropropagation. Unlike most other firms working in the micropropagation area that use tissues obtained from buds, Agriforest specializes in the culture of root tissues. The firm has used this method to produce fruit trees, assorted varieties of fruit plants, ornamental plants and a new product just recently put on the market called "Roselets." Agriforest has also developed a technique for the micropropagation of woody species which has been patented in Canada, the United States, Holland and Belgium. A micropropagation method for the reproduction of superior strains of Douglas fir and white pine is also being developed.

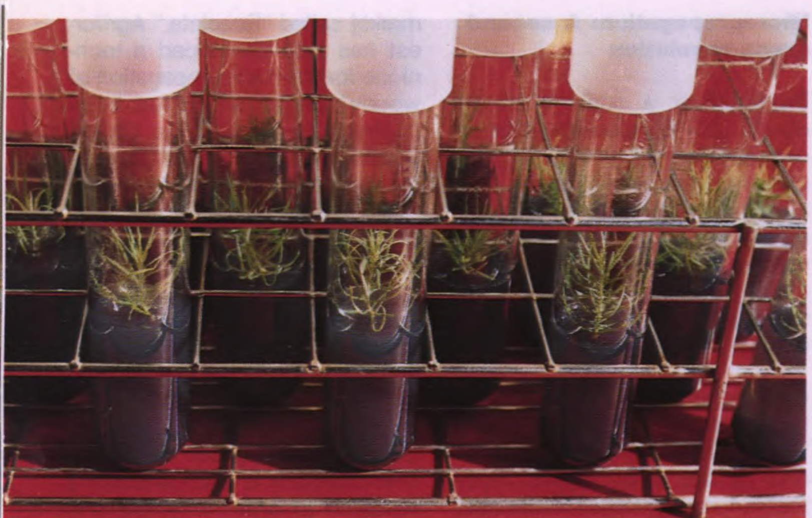
Les Clay & Son Limited of Langley, British Columbia, has already marketed about 400 different cultivars obtained by micropropagation in various countries throughout the world. This company is also conducting research in order to select and propagate various species of ornamental and forest plants on the basis of tissue culture.

High-performance biological fertilizers

Research in biotechnology has led to the discovery of micro-organisms that can be grown and used as actual living fertilizers.

These micro-organisms (bacteria or fungi) bond with the plant roots in order to retain atmospheric nitrogen (as in the case of bacteria of the *Rhizobium* genus), provide them with minerals essential to their growth (as in the case of mycorhiza) or facilitate plant growth and help control diseases, as in the case of rhizobacteria. Thus, in the field, these micro-organisms take over and take on the work of the farmer and fertilizers — all without cost!

Microbio-Rhizogen Corporation of Saskatoon, Saskatchewan, produces and markets rhizobium inoculants that can be used to grow assorted varieties of legumes, mainly peas, lentils, alfalfa, clover, etc. The Microbio-Rhizogen product is sold in a ready-to-use form. The firm is



Plant explants in the culture medium.
(Agriforest Technologies Ltd.)

Spring barley.
(Semico Inc.)

now conducting research in order to select the types of rhizobium that are compatible with lupin and chick peas.

Les Tourbières Premier Ltée, a Rivière-du-Loup, Quebec, firm that specializes in peat moss and peat moss-based products is interested in a type of mycorhiza (endomycorhiza) that forms a symbiosis in the plant root, where it bonds. The company is involved in the production of endomycorhiza and substrates compatible with their use. It has recently marketed a peat moss-based substrate that carries an endomycorhizial inoculum called Mycori-mix. This accomplishment is a first both nationally and internationally. The product can be used with market garden and ornamental commercial crops that use peat moss-based culture media. These crops consist mainly of market garden plants grown in greenhouses or transplanted in the field, especially celery, pepper, lettuce, tomato and cucumber, as well as plants obtained from *in vitro* culture, particularly apple trees, ferns and asparagus.

Genetic improvement of plants: Already a reality

Humans did not wait for biotechnology in order to start improving their crops, that is, to obtain cultivated plants with the most desirable characteristics, such as resistance to disease, early maturation or productivity. However, early attempts at plant improvement met with various problems. Genetic engineering can solve these problems by making it possible to change the genetic make-up of plants without involving sexual reproduction.

In the past, time was a major constraint, particularly the amount of time required to obtain a pure strain in a genetic improvement process. The Semico Inc. company of Sainte-Rosalie, Quebec, uses a technique called the "double-haploid method" to shorten the selection cycle of new cultivars of spring barley. It is now possible to create genetically pure plants from the second generation on. In comparison with the conventional genetic improvement process, this new technique makes it possible to jump 15 to 20 generations, thereby reducing the time required to develop a new variety of cultivar by four or five years.

W.G. Thompson & Sons Ltd. of Blenheim, Ontario, is also interested in the improvement of spring barley. Using the double-haploid technique, mainly with six-rowed spring barley, the company has been able to develop cultivars with valuable characteristics, such as good resistance to various diseases, strong stems with firm resistance to bending, and round, full, plump seeds.

Genetic engineering has also been used to develop genetically superior varieties of plants through different techniques. One of the most striking examples of this approach is the program for the genetic improvement of colza, a crop for which Canada is the largest world exporter, and which occupies a surface area of 1.2 million ha. Allelix Biopharmaceutical Inc. of Mississauga, Ontario, has managed to develop a genetically superior variety of this oil-producing plant. In 1987, the company announced that it now had colza plants that were both

Barley embryos cultivated in a nutritional medium — viable plantules.
(W.G. Thompson & Sons Ltd.)

male sterile and resistant to triazine, a herbicide that is normally toxic to colza.

This new variety was produced using a technique called "protoplasm fusion" or somatic hybridation, which consists of joining the contents of two somatic (nonsexual) cells obtained from plant tissue. This hybrid variety of colza is now being tested in the field, in accordance with government regulations. However, Allelix announced in 1989 that it had been able to develop the first plants of hybrid corn by using a sophisticated genetic engineering technique — the culture of immature male pollen (microspore). Thus, the firm was able to do with corn what had already been done with colza, but using a different technique. The pollen culture technique, which makes it possible to transfer laboratory results more quickly into the field, is likely to replace the use of protoplasm fusion.

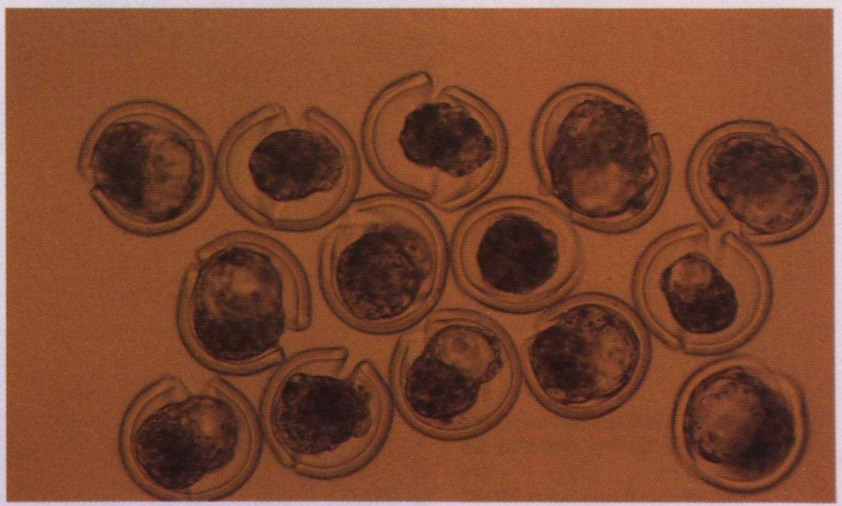
The next stage in colza improvement will undoubtedly involve genetic transfer, which has already produced very encouraging results in the laboratory.

Furthermore, the colza family encompasses a wide variety of genetic characteristics that can easily be exchanged among its members, such plants as broccoli and cauliflower. Indeed, Allelix researchers have recently been able to transfer the characteristic of male sterility from colza to broccoli, and they are now attempting the same process with cauliflower and cabbage.

Breeding success in livestock

Another area where biotechnology is being applied is animal breeding. The animal breeding techniques used in Canada are among the most advanced in the world, and Canadian Holstein cows are renowned as one of the most productive milk-producing breeds.

Biotechnological progress in animal breeding has led to the



Clone of 14 embryos ready to be transplanted into a cow.
(Alta Genetics Inc.)

development of useful embryo manipulation techniques, such as overovulation, the removal of embryos, the freezing and division of embryos, etc. Alberta Livestock Transfers of Calgary, Alberta, which has recently become Alta Genetics Inc., was one of the first companies in the world to use embryo manipulation techniques on an industrial scale. In addition, the company has built a significant export market for its frozen embryos.

Alta Genetics has become the standardbearer and is a leader in cloning and nucleus transplantation methods, particularly with Holstein dairy cattle. In collaboration with the University of Calgary, the company is also conducting research on more advanced genetic manipulation techniques, such as gene transfers. Research results may lead to more productive and healthier animals more suitable for use as food or for industrial purposes. However, at present, gene transfer, particularly for large animals, is one of the techniques that has yet to be fully mastered.

Four Holstein calves obtained from the same clone and delivered using the nucleus transplantation process.
(Alta Genetics Inc.)

Developing Aquaculture

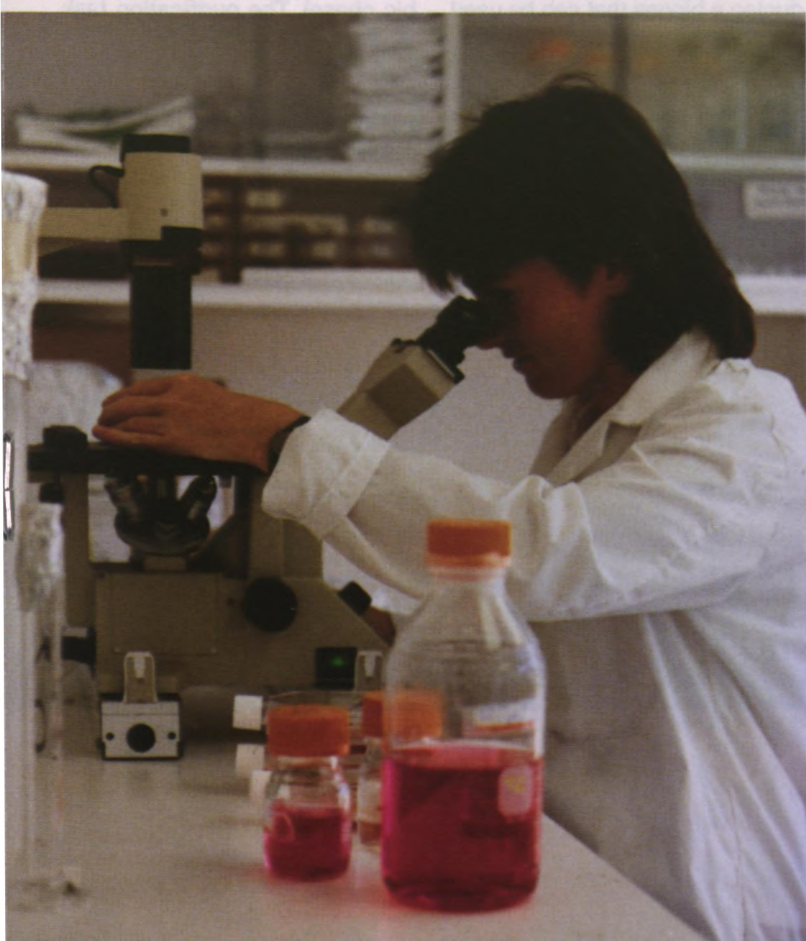
Salmon eggs where the eye is visible. Ovulation and egg-laying are stimulated by the injection of "Ovaprim," which is a reproductive agent prepared from peptide hormones and used with salt- and fresh-water fish.
(Syndel Laboratories Ltd.)

Although aquaculture is a new industry in Canada, it holds considerable promise for successful development. Techniques derived from biotechnology will undoubtedly help bring about a major breakthrough in the next few years.

Syndel Laboratories Ltd. of Vancouver, British Columbia, has mastered the art of stimulating ovulation and egg-laying in farmed fish. The company has also recently marketed a very sophisticated product called Ovaprim, used mainly with carp, salmon and catfish. A fourth-generation product prepared from peptide hormones (godanotropin and dopamine), Ovaprim is the result of years of research. The use of extracts of pituitary hormones to control the reproductive process has become a thing of the past, and today Syndel Laboratories is one of the world leaders in new techniques used to induce ovulation in salt- and fresh-water fish.

Another company in British Columbia, Microtek Research and Development Ltd., is interested in developing diagnostic tests and vaccines for various diseases that can affect fish in aquaculture farms. Microtek has developed a vaccine, approved by Agriculture Canada, as well as a diagnostic test for various fish diseases. This research and development firm has also developed a monoclonal antibody to identify *Renibacterium salomoninarum*, a bacterium responsible for kidney disease in salmon.

Royal Pacific Sea Farms Ltd. of Vancouver, British Columbia, is concentrating its efforts on growth hormones, in particular recombinant somatotropin. With this hormone, the company aims to improve the productivity of fish farms.



Tissue culture laboratory used to carry out diagnostic tests of viral diseases in fish.
(Microtek Research and Development Ltd.)

Over the medium term, the environment will likely derive great benefits from the advances being made in biotechnology. Already, it is possible to produce very effective bacteria to purify waste water and biologically degrade toxic waste.

Use of micro-organisms to purify waste water

The biological processes used to purify waste water are based on the presence of bacteria that develop naturally. With or without oxygen, depending upon the process, these bacteria decompose the organic materials contained in the water and use them as a source of food. The residues are concentrated in the form of sludge, which is then ready for disposal.

Faced with an overload of organic materials, which often occurs in purification plants, ordinary bacteria cannot meet the challenge. However, a new process known as LLMO (Liquid Live Micro-Organism), which has already been approved in the United States, provides a remedy for the problem. Aquarecherche Ltd. of North Hatley, Quebec, has given the name of DACTAPUR to its version of the LLMO process. It was used for the first time in Canada during 1987 in the purification plant of the Municipality of Lac-Mégantic, Quebec.

This process is of considerable interest because it adds a mixture of non-pathogenic super-bacteria strains to the waste water. These can help service micro-organisms significantly reduce (in the order of 30 to 50 per cent) the volume of sludge produced during processing, while making the residues available for agricultural and forestry purposes. In addition, these super-bacteria digest fats and eliminate the problem of unpleasant odour in waste-water networks. Aquarecherche investigators have also been able to condition these bacteria so that they can degrade solvents and hydrocarbons.

Paques Lavalin of Willowdale, Ontario, a company very active in the environmental field, is especially interested in the anaerobic processing of waste water. This technology, which was imported from Holland, has made it possible to develop the BIOPAQ system, which can be used to process waste water while producing a biogas that can be used to replace conventional fuel in a plant. The anaerobic bacteria used in the BIOPAQ reactor digest up to 90 per cent of the biodegradable materials contained in waste water. Apart from waste-water processing plants, the BIOPAQ system can be used in various other industries, in particular pulp and paper, food products and beverages.

At the same time, it is clear that industrial effluents are very dangerous for the environment, particularly the aquatic environment and the water table. Industry is becoming increasingly aware of its role in protecting the environment and of the possibilities offered by biotechnological processes. Such is the case with the Bon-Conseil cheese-making plant, a Quebec subsidiary of Agropur. The plant dumps a volume of waste water equivalent to that produced by a population of 50 000 people.

Aware that agri-food effluents have been identified as a major pollutant, the company has distinguished itself by acquiring a waste-water processing centre that uses a mixed anaerobic-aerobic system. The initial decomposition of the polluting load is obtained by means of bacteria that act in a sealed chamber in the absence of air (anaerobic phase). The purification task is complemented by the activity of aerobic bacteria contained in outdoor tanks in the open air. The sludge produced by the process is used as a fertilizer for an experimental spruce nursery next door to the waste-water processing centre.

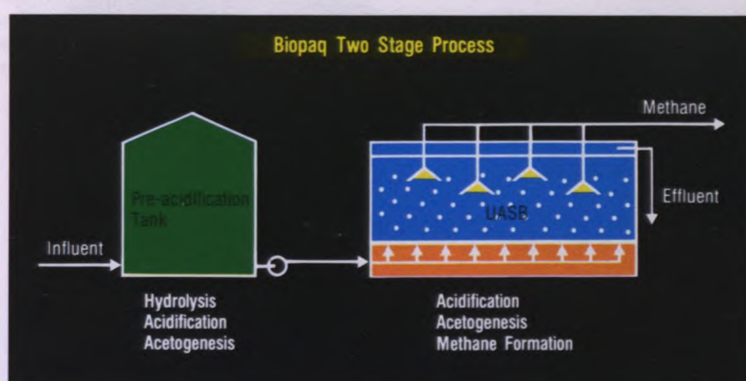


Illustration of the BIOPAQ system.
(Paques Lavalin)

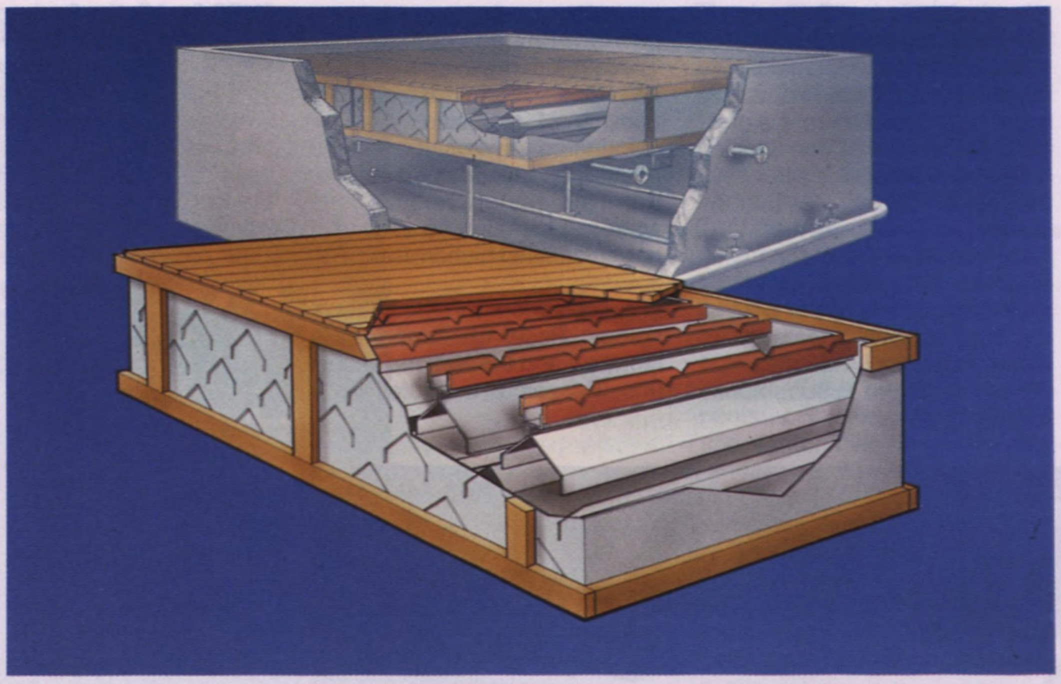


Illustration of a gas/water separator module in the foreground and the reactor container in the background.
(Paques Lavalin)

Sample of horsetail grass (*Equisetuum fluviatile*). This semi-aquatic plant can concentrate arsenic in its tissues and is used to determine the level of arsenic concentration in laboratory and pilot studies.
(P. Lane and Associates Ltd.)

Among the companies that concentrate research and development in this area, of particular interest are P. Lane and Associates of Halifax, Nova Scotia, and ADI Ltd. of Fredericton, New Brunswick. P. Lane is mainly concerned with the microbial degradation of aromatic polycyclic hydrocarbons that contaminate the soil and water, and with the accumulation of heavy metals in aquatic macrophytes. The company orients much of its research toward the needs of developing countries. ADI is the only small business in Canada involved in biotechnology projects at the international level. Anaerobic waste-water treatment for warm, strong organic waste water coming from a wide range of sources is of particular interest to ADI.

Heavy metals and toxic products: Bacteria that can control them

One of the most promising applications of biotechnology in the environmental protection area is the biological degradation of toxic waste through microorganisms. Toxic waste often causes great damage before it is detected.

To address this problem, CBR International Biotechnologies Corporation of Sidney, British Columbia, has developed and is now marketing an "Environmental Monitor" test that can be used to measure environmental stress in living organisms, especially micro-organisms. There is a great need for tools that can predict, detect and diagnose environmental deterioration.

The environment is constantly attacked by a wide variety of toxic compounds of the organochlorine family. However, a recent discovery indicates that certain strains of *Pseudomonas* bacteria can decompose some polychlorinated compounds. These micro-organisms produce enzymes that destroy the nucleus of molecules of polychlorinated hydrocarbons and release the chlorides that render the molecule toxic. This approach can also be used with polychlorinated biphenyls (PCBs).

In collaboration with the Biotechnology Research Institute in Montreal and the National Scientific Research Institute-Health (INRS-Santé), the Sanivan Group of Anjou, Quebec, is developing a PCB biodegradation process. This initiative will require extensive effort and rigorous research protocol, but tests have already been carried out in the field and the Sanivan Group expects that a biological decontamination process could be available at the beginning of the 1990s.

Class 100 Clean Room for the determination of trace levels of environmental contaminants.
(CBR International Biotechnologies Corporation)

Maximizing the Biomass

Fermentation equipment.
(Iogen Corporation)

The development of biotechnologies can significantly affect the processing and profit-making capacity of industrial waste.

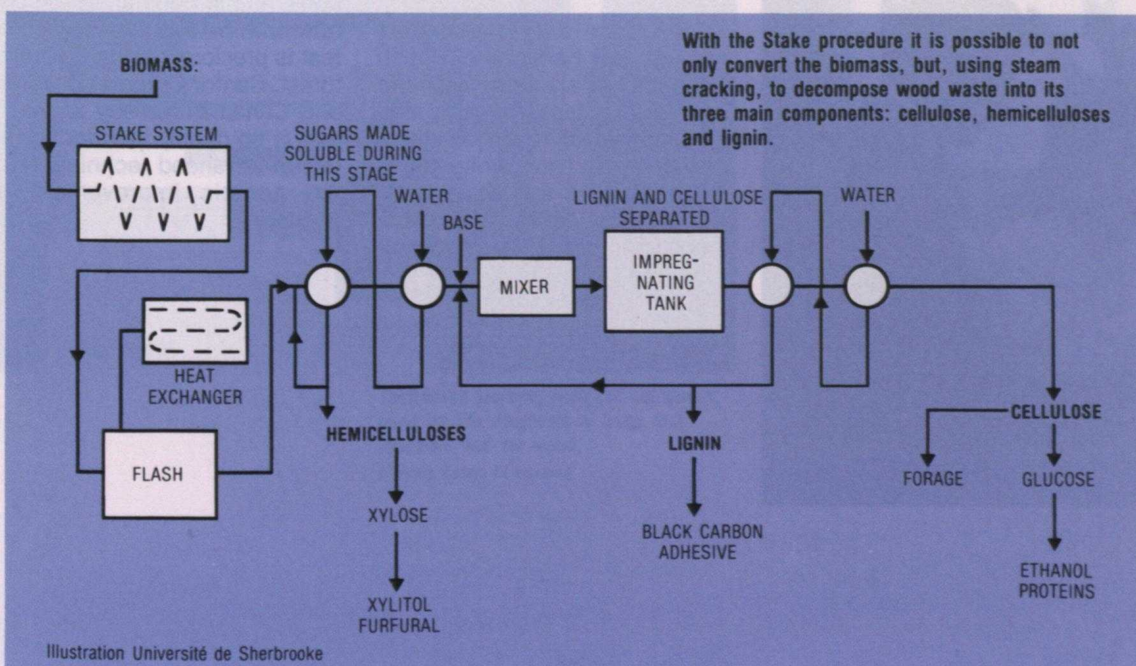
To deal with wood waste produced mainly by the forestry and agricultural industries, Stake Technology Ltd. of Norval, Ontario, has developed a steam cracking process for biomass transformation. This process, called Staketech, uses steam cracking to decompose waste into its three principal components: cellulose, hemicellulose and lignin. With the Staketech process, Stake has become a world leader in the conversion of lignocellulose material. However, this is only the first stage in the transformation of biomass components into a whole range of valuable products, and it is at this point that biotechnology will play a role.

Micro-organisms can, for example, metabolize the sugars contained in hemicellulose and thereby obtain a protein-rich product that can be used as animal feed. The chemical and food industries could also take advantage of hemicellulose byproducts, the former with the production of furfural, a solvent; and the latter with the production of xylitol, a byproduct of wood alcohol (xylose) that has an excellent sweetening power and can be found mainly in sugar-free chewing gums.

In regard to xylitol, Iogen Corporation of Ottawa, Ontario, has developed a production technique that can reduce costs significantly. When produced conventionally, xylitol is 500 per cent more expensive than when it is obtained from sugar alcohol and sorbitol.

Cellulose can be hydrolysed by enzymes in the preparation of fermentable sugars that can be used to produce ethanol or prepare complex chemical products (acetone-butanol, polyols, etc.).

The lignin obtained with the Stake process is not chemically modified. Thus, it could be used in the preparation of adhesives for the forest products industry and in a wide variety of other products.

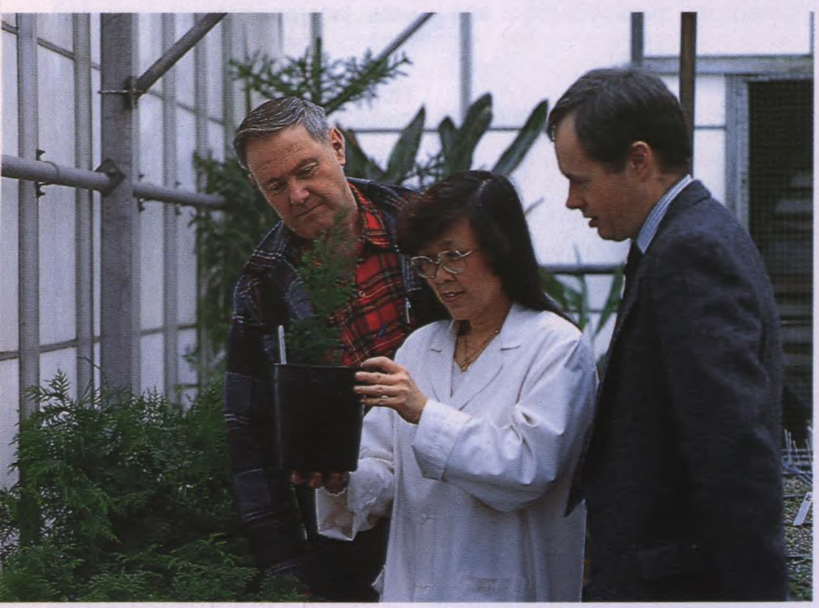


With the Stake procedure it is possible to not only convert the biomass, but, using steam cracking, to decompose wood waste into its three main components: cellulose, hemicelluloses and lignin.

Biomass conversion process.
(Stake Technology Ltd.)

Encouraging Forest Growth

A number of plantules are produced in test tubes from a single yellow cedar plant.
(Canfor Corporation)



The micro-shoots are then transplanted into the soil in the greenhouse, until they can be transplanted outside.
(Canfor Corporation)

One of the major contributions of biotechnology to forest health and growth is undoubtedly the successful association of mycorhizal fungi and trees. It has been shown that mycorhiza improve the chances of survival of young plants by allowing them to better absorb water and mineral salts (particularly phosphorus) and by providing them with some protection against pathogenic agents.

The Rhizotec company of Saint-Jean-Chrysostome, Quebec, marketed three mycorhizal inoculants in the course of 1988 and became the first Canadian firm to succeed in this sector. In the three cases, the fungus used was *Laccaria bicolor*, an edible fungus that is routinely consumed as food. This company also developed a technique for the inoculation of plants in containers, a method that makes it possible to inoculate 20 000 plants per hour. Rhizotec has a bank of 152 different strains of mycorhizal fungi and is in the process of producing approximately 12 on a commercial basis.

Balco Canfor Reforestation Centre Ltd. of Kamloops, British Columbia, is also very active in this area of biotechnology and produces about 10 million plants per year, mainly white pine, lodgepole pine and Douglas fir. The nursery uses mycorhizal fungi to improve the quality of the plants and the rate of survival after planting. Various experiments have in fact shown that the rate of survival of the plants could be increased by about 25 per cent. The rate of growth of mycorhized trees is also higher.

Within the framework of its genetic improvement program, Canfor Corporation of Vancouver, British Columbia, an affiliate of Balco Canfor Reforestation Centre Ltd., has developed "super-trees," or hybrids, that grow faster and produce wood of better quality.

Moreover, in collaboration with Les Clay's nursery of Langley, British Columbia, a project is under way to culture tree tissues in order to produce clones of high-quality conifers and reproduce them quickly through micropropagation. This technique has been successfully used with yellow cedar, and studies are being carried out with other species, such as Douglas fir and sitka spruce. These efforts are expected to improve by 10 per cent the yield of future plantations, and in general, tissue culture and cloning will save time that is precious for the Canadian forest. Canfor Corporation is the only Canadian forestry company that is so deeply involved in the use of advanced techniques for the genetic improvement of conifers.

Improvements in Wood Processing

In addition to offering promising possibilities for the quantitative and qualitative improvement of forest production, biotechnology can also play an important role in wood processing.

It is already known that some micro-organisms, particularly enzymes and fungi, can transform the main components of wood (cellulose, hemicellulose and lignin) into a wide range of substances — chemical products, solvents, food products and fuels. Now, however, the challenge is to find the most effective micro-organisms and the most productive and economic techniques to achieve these results.

Technician working with the equipment used for the diagnosis of fungi that discolour and rot wood.
(Forintek Canada Corporation)

Iogen Corporation of Ottawa, Ontario, has unique and significant experience in the production of cellulases, enzymes that have been selected to modify or completely break down cellulose fibres to make a useful wood component. Many types of cellulases are available, namely endoglucanase, exoglucanase and betaglucosidase. Iogen was the first company to develop an enzymatic conversion technique that allows the conversion of cellulose into glucose.

Forintek Canada Corporation of Ottawa, Ontario, has identified an enzyme, xylanase, that can play a role in the process used to bleach pulp for fine papers. The pulps treated with xylanase require fewer chemical products and produce better yields. Forintek has obtained a patent for the production and purification of xylanases on a large scale.

In the Pulp and Paper Research Institute of Canada (Paprican) in Pointe-Claire, Quebec, researchers have also discovered a fungus, *Coriolus versicolor*, that can bleach kraft pulp obtained from hardwood within a period of five days under aerobic conditions.

In the lumber field, Forintek Canada has developed a test for the diagnosis for biological control of fungi and sap-staining fungi that can affect the colour of wood. The wood could simply be inspected using an immunological test to detect infected wood that has not yet been discoloured and should be treated. The conventional method used to protect the wood against colour changes uses chemical products that are toxic to living organisms and can remain in the environment, whereas the treatment developed by Forintek is based on the natural competition that exists between fungi. Thus, some fungi that do not change the colour of wood or lead to rotting are used to prevent the development of undesirable fungi. This less toxic treatment may meet the environmental standards in force in the lumber export markets.

Mining with Bacteria

Bacteria colony (*Thiobacillus ferroxidans*) of leaching microbes (electron micrography X 7500). These bacteria digest pyrite or iron sulfide and release the precious metals.
(GB Biotech Inc.)

The largest biological leaching reactor in the world. The tank measures 6.5 m in diameter and 7.2 m in height. This reactor is located near Goldbridge in British Columbia.
(GB Biotech Inc.)

The history of bacteria for use in the mining industry began in 1947 when two researchers in British Columbia attempted to explain why abandoned coal mines produced acid concentrations. They discovered that a bacterium, *Thiobacillus ferroxidans*, exists at the bottom of a mine. This bacterium can accelerate, by hundreds of thousands of times, the natural conversion of pyrite into sulphuric acid. This process, called metal bioleaching, can be used to release precious metals contained in the pyrite.

GB Biotech Inc. of Burnaby, British Columbia, is one of the two or three world leaders in the use of bacteria for the concentration of gold and silver ores. The concentration operation is carried out in a reactor. The company has built the first biological leaching plant in North America to recover gold and silver from ore and concentrates with a low sulphur content. The biological leaching process developed by GB Biotech is now being marketed, and the company expects eventually to use the same process in the open air, spraying the bacterial solution over ore piles.

Coastech Research Inc. of North Vancouver, British Columbia, is involved in research and development in the mining field and offers its services to the mining industry. Among other aspects, the company is interested in the use of micro-organisms for the extraction and recovery of metals from ore, concentrates and mining waste. The firm works mainly on the biological leaching of gold, but it is also interested in copper and other metals.

With government support, Denison Mines Limited of Elliot Lake, Ontario, has been successful in developing a biological leaching process that can be used for the underground extraction of uranium.

Bacteria could also be used to eliminate mining waste, a source of pollution mainly because of its sulphur content. Recbiomine Inc. of Sainte-Foy, Quebec, has installed a pilot laboratory to develop a process for the biodegradation of mining waste. The company expects to market this process in due course.

Glossary

Antibodies
Blood proteins that serve as the basis of the immune system in mammals. Antibodies combine specifically with corresponding foreign substances called antigens (see antigen).

Antigen
Molecule (generally a protein) which, when introduced into the body, stimulates the production of antibodies that react specifically with this antigen.

Bacterium
Very common unicellular organism that measures about one micron. Some bacteria are pathogenic, but the majority are useful to man for a large number of natural processes.

Biosynthesis
The production of a chemical substance by a living organism.

Cellulase
Enzyme that decomposes cellulose into glucose.

Cellulose
Polysaccharide made up of glucose units that are joined together. Cellulose makes up the greatest proportion of the walls of plant cells.

Clone
Group of cells that are all derived from a single initial cell through successive divisions.

DNA
Deoxyribonucleic acid present in the nucleus of the cells. It contains the chromosomes and is the basis of heredity.

Enzyme
Protein molecule that acts as a catalyser (accelerator) of biochemical reactions that take place within living organisms.

Fermentation
Process that provides energy through the (incomplete) degradation of organic materials in the absence of oxygen.

Gene
Portion of a DNA molecule that encodes the amino acid chain forming a protein.

Genetic code
Hereditary information used to assemble the basic fundamental constituents of living beings (proteins) and control basic living reactions.

Genetic engineering
Biotechnology used to change the hereditary information of a living cell in order to make it accomplish different functions. Genetic engineering is used for cellular "reprogramming."

Genetic manipulation
The process of adding a gene to a cell in order to provide it with a new characteristic. To do this, it is necessary to remove the desired gene from an animal cell and transfer it to a bacterium.

Genome (or genetic inheritance)
Set of chromosomes in a cell.

Hemoglobin
Protein molecule containing iron that has the ability to capture oxygen in a reversible manner and thus transport it throughout the organism. Hemoglobin is contained in the red blood cells.

Hormone
Substance secreted by an internal secretion or endocrine gland; it is emptied into the blood and is carried to the tissues, where it carries out a specific action.

Hybrid
A new variety of plant or animal that results from crossing two existing varieties.

Hybridation
Reaction consisting of realigning two complementary strands of DNA.

Hybridoma
A hybrid cell formed by the fusion of a lymphocyte and a myeloma (or cancerous) cell. Hybridomas are used mainly for the production of monoclonal antibodies.

In vitro
A biological experiment that takes place outside a living organism.

Interferon
Natural anti-viral (and probably anti-tumour) protein secreted by the attacked cells.

Lymphocyte
Small white globule that produces antibodies (lymphocyte B) or plays a role in the amplification of immune mechanisms (lymphocyte T).

Metabolism
Chemical reactions that take place in a cell and, by extension, the reactions that take place in a living organism to produce energy.

Molecules
Combinations of atoms joined together by chemical bonds. The average size of a molecule is 10 times greater than that of an atom.

Monoclonal antibodies
Very specific antibodies obtained by hybrid cellular strains called hybridomas (see hybridoma).

Moulds
Microscopic fungi visible to the naked eye.

Mutation
Alteration of DNA structures by a physical or chemical agent. Anything that can produce a mutation is said to be a mutagen. Alterations produced by mutations are hereditary.

Oncogene
A gene that plays a role in the transformation of normal cells into cancerous cells. Some viruses are oncogene carriers.

Pathogen
Something that causes disease: pathogenic microbe.

Photosynthesis
Reaction through which chlorophyllic plants transform light energy into organic substances.

Polymer
Long chain macromolecule formed by a repetition of small structural units.

Porphyrin
Essential biological pigment (e.g., chlorophyll, red blood corpuscles).

Protein
Macromolecule formed by a chain of amino acids that are joined together. They are the building units of all living beings. The proteins that catalyse the metabolic reactions are called enzymes.

Restriction enzymes
Particular enzymes, present in all cells, that are capable of recognizing and destroying DNA. Restriction enzymes are used in genetic engineering as biological "scissors" to cut the DNA and recombine it with other fragments.

Yeasts
Single-celled fungi.

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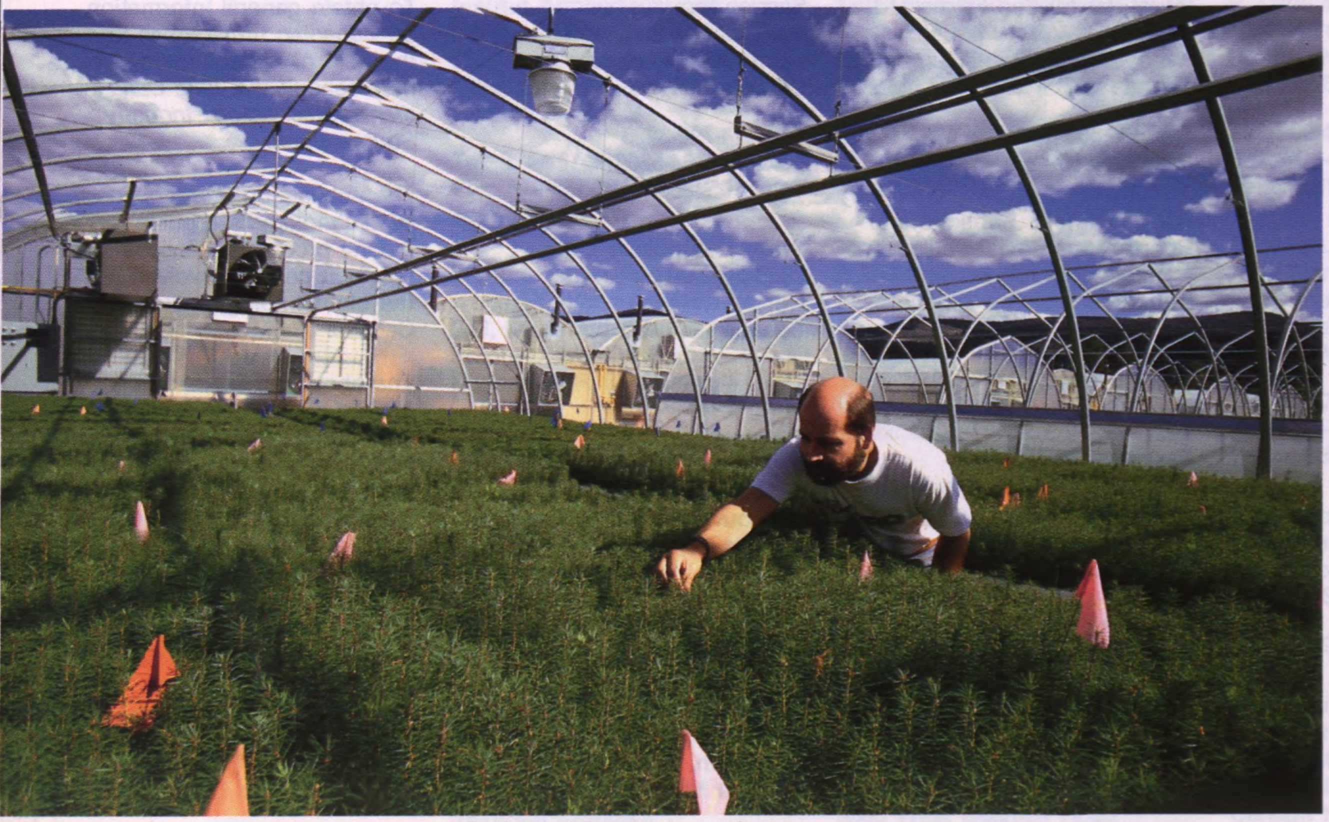
To obtain general information on Canadian firms active in the field of biotechnology, you may consult the *1988 Canadian Biotechnology Industry Source Book*.

The publication *Partnerships in Biotechnology* is a guide to federal programs, services and research centres involved in the biotechnology industry in Canada.

The above publications are available by writing to the Biotechnology and Health Care Products Directorate, Industry, Science and Technology Canada, 235 Queen Street, Ottawa, Ontario K1A 0H5.



Conifer plants growing in greenhouses.
(Balco Canfor Reforestation Centre Ltd.)

Production of vaccines using fermentation equipment.
(Microtek Research and Development Ltd.)

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