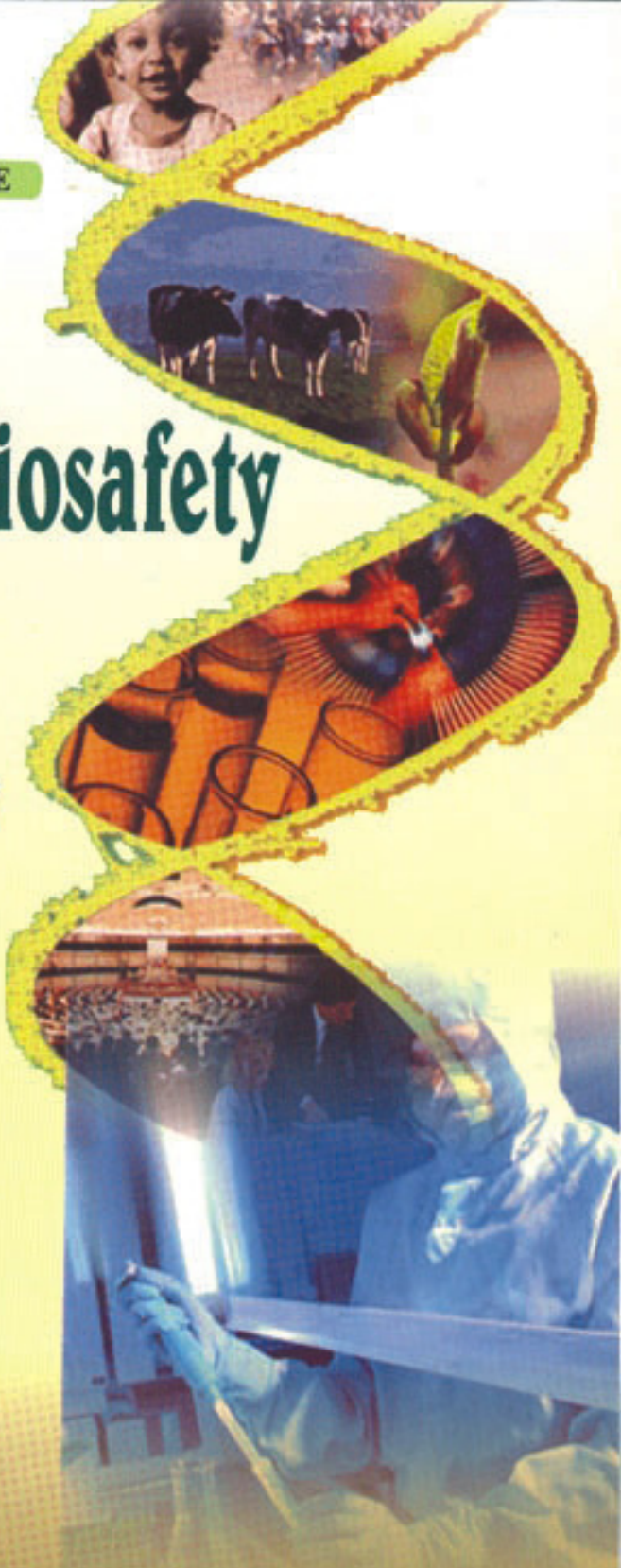
NEW AGE

Bioethics and Biosafety in Biotechnology



V. Sree Krishna

NEW AGE INTERNATIONAL PUBLISHERS

Bioethics and Biosafety in BIOTECHNOLOGY

THIS PAGE IS BLANK

Bioethics and Biosafety in BIOTECHNOLOGY

V. Sree Krishna
M.Sc. (Biological Sciences), Ph.D. (Plant Biotechnology)
Ph.D. (Marine Animal Biotechnology), M.B.A.
Professor and H.O.D. Biotechnology
Nagarjuna College of Engineering and Technology
Banaglore

PUBLISHING FOR ONE WORLD

NEW AGE INTERNATIONAL (P) LIMITED, PUBLISHERS

New Delhi • Bangalore • Chennai • Cochin • Guwahati • Hyderabad
Jalandhar • Kolkata • Lucknow • Mumbai • Ranchi

Visit us at **www.newagepublishers.com**

Published by New Age International (P) Ltd., Publishers

ISBN (10) : 81-224-2248-9

ISBN (13) : 978-81-224-2248-1

PUBLISHING FOR ONE WORLD

NEW AGE INTERNATIONAL (P) LIMITED, PUBLISHERS
4835/24, Ansari Road, Daryaganj, New Delhi - 110002
Visit us at **www.newagepublishers.com**

Dedicated to

my wife

Dr. S. Vijaya Sree

M.B.B.S., D.G.O.

THIS PAGE IS BLANK

Preface

Biotechnology and allied fields like Molecular Biology, Biochemistry and Microbiology are promising research-oriented and fast-growing interdisciplinary fields. These subjects find application in every sphere of life and have tremendous career opportunities available presently and in future.

In such demand-oriented fields, lot of research works at molecular level changes, like gene-transfer, stem-cell research, chemicals application, microbial involvement in environmental upgradation including organic shift is being aimed at fertilizers, raw materials and ultimately in human beings–food-related issues. Under these circumstances due to growing concerns arising from Genetically-Modified Organisms throughout the world the UNIDO/WHO/FAO/UNEP has built up an informal working group on Bioethics and Biosafety. In 1991, this group preferred the "voluntary code of conduct for the release of organisms into the environment". Such operative Biosafety guidelines and Bioethic regulations are incorporated in this book in accordance with the syllabus of M.Sc. (Biotechnology), B.E. (Biotechnology) and B.Tech. (Biotechnology).

I thank Mr. Saumya Gupta, M.D., M/s. New Age International (P) Ltd., Publishers and the Production Editor for their kind cooperation. My sincere thanks to Mr. Sudharshan, S. P. and Mr. Srinath, Manager, M/s New Age International (P) Ltd., Bangalore Branch.

V. Sree Krishna

THIS PAGE IS BLANK

Contents

Unit-1

Unit-2

Unit-3

Unit-4

Unit-5

THIS PAGE IS BLANK

Unit 1: An Overview of the Legal and Socio-economic Impacts of Biotechnology—Biosafety Regulations

Biosafety, as currently discussed in the International "Convention on Biological Diversity" (CBD) and designed to create internationally binding protocols on biosafety.

The application of biotechnology to food and agriculture can bring not only potential risks and benefits as any technology can, but also concerns about the human dimensions coupled with biotechnology. These include both positive and negative impacts on stake holders, social institutions, economy and communities.

Different areas associated with biosafety include:

(*i*) Agriculture and food system issues

(*ii*) Market and consumer issues

(*iii*) Institutional issues, business issues and

(*iv*) Social issues

Agriculture and food system issues. These include the impact of biotechnology on the organisation, structure and behaviour of agricultural industry; further, the coexistence of conventional organic and biotechnology oriented agriculture; the capacity of the food system to segregate genetically-modified commodity and product of specific markets; impacts on competitions involved, trade in agricultural commodities and the economical impacts of establishing oversight, standard regulations and public policies concerning biotechnology.

Market and consumer issues. These include various limitations which come to the rescue of consumer demand for overall against the products of agricultural biotechnology, the needs, desires and concerns of consumers in domestic and international markets; the influence of culture, advertising, product labelling, scientific information and recent new events on consumer decision making about the use of biotechnology products; different methods for most effectively increasing the understanding on which publication and primary decision making concerning biotechnology is based.

Institutional issues and business issues. These include the impacts of biotechnology on individual forms or group of forms about buying or selling biotechnology products and processes; changes in business practices, alliances and domestic and international markets including markets in Third World countries.

Social issues. These include the needs of various public to secure meaningful information for involvement in decision making on development and by use of agricultural biotechno-logy; the role of civic engagement at the local, state and national levels; perceived and actual risks-benefits to consumers and the general environmental protection, agro-terrorism; research vandalism, and their impacts on Third World nations.

NATIONAL AND INTERNATIONAL LEVEL BIOSAFETY REGULATIONS

In most of developing countries, biosafety regulation is still in its infancy. Appropriate biosafety regulations are one of the prerequisites for a successful transfer of biotechnology to and, among developing countries. Important issues in the debate on biotechnology regulation are the uplifting of field trials, systematising of regulations, and capacity development in developing countries.

The regulation of biosafety is a tool for the safe deployment of biotechnology applications into the environment. It is rather a specialised form of Environmental Impact Assessment (EIA), focussing on the biological consequences of applying Genetically Modified Organisms (GMOs). As a part of EIA, the nature of the organism, the environment in which the organism is to be released, and the interaction of such species, with reference to intraspecific and interspecific are to be analysed. Field trials constitute a major part of the transgenic plants impact assessments, however, biosafety concerns all Genetically Modified Organisms (GMOs).

TRIALS ON–FIELD

Among several industrialized countries, biosafety regulations have been implemented since the mid 1980s; however, there are significant differences among some of these countries. Good experience has been established, both in the regulatory process as well as in analysing the environmental impact of transgenic crops through small demonstration trials. Until December 1992, more than 1,180 small-scale demonstrations with transgenic plants have been conducted in countries having Organisation for Economic Cooperation and Development (OECD). Further, these trials are also conducted to test the expression of the newly-induced trait.

The most commonly tested traits in those demonstration trials are resistant to herbicides, viruses and insects. Herbicide resistance alone accounts to 40 percent of the total number of trials. This high percentage attracts both scientific and commercial interests. In research on transgenic crops, herbicide resistance genes are often used as marker genes for the selection of successfully modified plants. At the same time, commercial interest for herbicide resistance draws from agrochemical companies seeking new markets or safeguarding the existing market shares for their herbicides.

UPSCALING OF FIELD TRIALS

The ecological risks of transgenic crops depend on relatively rare events occasioned by the interaction of particular plants with a particular environment. According to a report of the US Union of Concerned Scientists (UCS), commercial use on a large scale increases the opportunities for the rare harmful conjunctions of factors to occur. Even if a large number of small scale demonstrations are conducted, their outcome does not predict necessarily safety on a commercial scale. The number of plants involved in commercial use is in order of magnitude larger than the number involved in field tests. Most of the field tests involve not more than 4 hectare plots. In contrast, commercial use of major crops such as maize and soya beans could entail cultivation on millions of hectares in the United States alone.

Usually field tests are conducted under conditions that severely limit the escape of plants or genes from the test plots. For example, test sites are far removed from other crops or wild relatives with which the transgenic crop can interbreed. Developing countries, however, host many wild relatives of crop plants. Also, sites are monitored to detect transgenic plants that escape. However, no such restrictions apply to commercial use. Once available in the market, engineered plants are free to migrate away from the farm, and their pollen may flow unimpeded to relatives in agricultural and non-agricultural habitats.

Compared to field tests, commercial use will involve crops cultivated in far more diverse environments, in proximity to a broader selection of relatives in different climates, and subject to a greater variety of weather events, such as floods and hurricanes. Floods can expose seeds and plants to many new, potentially congenial environments.

The UCS report offers a framework and guidelines for analyzing the environmental risks of large scale, commercial use of transgenic crops. On discussing the issue of upscaling within the OECD, the OECD has developed a set of scientific principles for the environmental safety of the large scale use of transgenic plants. These guidelines contend that experience and knowledge gained by traditional plant breeding is essential. The more that is known about a given plant, its traits, its environment and their likely interactions, the easier risk/safety analysis and subsequent risk management will be harmonization.

Many non-governmental organizations, bilateral and multilateral agencies are presently involved in providing direction and assistance in developing appropriate regulations and technical expertise for implementing them. One of the major issues in these international initiatives is harmonization of regulation. Harmonization means that regulatory requirements are made compatible and that reviews are made consistent with each other. However, it does not mean that all countries should have identical policies, priorities or strategies. The aim is uniformity in requirements for data collection and testing procedures, and the exchange of information. Eventually, the outcome of national regulations depends on public perceptions, and public acceptance, as well as on cultural and institutional processes.

Harmonization of regulations has several advantages :

(*a*) Regulatory authorities may benefit from experiences in other countries, both on the organization and the content of risk analysis.

(*b*) It may foster technology transfer as it installs confidence and simplifies the preparation of field trial applications, and

(*c*) It may protect developing countries from being used as a testing ground for field trials that would not be permitted in other countries.

DEVELOPING COUNTRIES

The developing countries, however, do not have regulatory or monitoring procedures, mainly due to lack of monetary enforcement systems, including inadequate institutional facility. India and Philippines which have established regulations and incorporated in their national laws, are exceptions. Other countries *viz.,* Argentina, Bolivia, Brazil, China, Colombia, Costa Rica, Cuba, Indonesia, Malaysia, Thailand and Zimbabwe are in a more or less advanced stage of drafting resolutions, or have formed adhoc committees. Adhoc committees are generally formed to review field trial applications for transgenic plants. Although the number of field trials cannot be matched with that of the OECD countries, it is gradually increasing. In the last three to four years, in Latin America alone, over 60 field trials have been conducted.

COORDINATION AND CAPACITY ESTABLISHMENT

Many of the developing countries are in a process of designing and implementing biosafety regulations. This stage enables opportunities for international coordination of national approaches. Such coordination is carried out by the Inter-American Institute for Cooperation on Agriculture (IICA), for several regions within Latin America, and the International Service for the Acquisition of Agribiotech Applications (ISAAA) for certain selected regions. Harmonization *i.e.,* the regulatory requirement issues were discussed at the "African Regional Conference for International Cooperation on Safety in Biotechnology", held in Zimbabwe in October 1993.

The harmonization processes of IICA and ISAAA are mainly a process building endeavour, since regulation is only as good as the public who develop and enforce it. Thus, capacity building can be defined as (*i*) the training of those nationals who will be developing and implementing biosafety regulatory mechanisms and (*ii*) the sharing of experience with agencies that are already for many years involved in developing and implementing such regulations. This can be achieved through intensive workshops that would enable participants to gain hands on experience pertaining to the issues and procedures.

There is also a clear-cut way in establishing and harmonizing biosafety regulations in developing countries, by transnational biotech companies. Firstly, if a regulatory system is in place, companies can share responsibility with regulatory authorities in case something misfires. Secondly, supporting regulation may provide a chance to influence the content of the regulation. And finally, implementing and harmonizing regulation can avoid unfair competition from companies established in countries without strict safety regulation. As this is interesting and attractive several international biotech companies contribute to the ISAAA initiative.

SCREEN — A NEWSLETTER ON BIOSAFETY

The European Union has decided to sponsor a newsletter, SCREEN (Swift Community Risk Evaluation Effort Network), on the release and regulation of genetically-modified organisms, to facilitate the flow of information between the European countries national authorities, and scientists including regulatory bodies. In a later stage, the newsletter will focus on the safety of GMOs-related foods and intellectual property protection. Although this newsletter is European region centric, biosafety matters of other parts of the world are also discussed and published in it. SCREEN is available free of charge. Recipients are expected to reciprocate by contributing annually half a page describing their activities on biosafety. Applicants other than European region are evaluated on their involvement in biosafety monitoring.

RISKS VERSUS BENEFITS

The risk assessment procedures of transgenic plants should provide scientific quantitative information about the chance of any adverse effect leading to an hazard. This information can be gathered through field trials/demonstrations. There is a process of assessing these field trials. This is the state of balancing risks against benefits. In this assessment, ecological effects are to be mainly evaluated. Risk acceptance depends on several factors *viz.,* the expected benefits, product kinds involved, different possibilities to prevent risks and the need for innovative products through latest technologies. Public perception and reliability of information providing agency, on risks and benefits, also are important. The evaluation of potential risks against expected benefits may vary among different countries. In the application of biotechnology for food production, industrialized countries can easily afford to place higher priority on health and environmental quality management; whereas, developing countries have to concern more with the production and distribution of food. If the application of biotechnology provides enhanced food supplies, developing countries shall accept certain ecological risks. More often the difference is not between south and north, but between entrepreneures and consumers and between biotechnologists and environmentalists. As entrepreneurship is risk oriented, entrepreneurs may accept certain risks than consumers. Consumers can “wait and see”; if their risk perception of some product is too high, they can decide not to buy that product. Biotechnologists focus on the genes of an individual plant and claim that genetic engineering has opened wider options for improvement of plant production. Environmentalists focus their attention on the

effect of transgenic plants on ecosystem. Thus, the acceptance of risk and the evaluation of risk against benefit is very much influenced by the position and interests of producer and consumer. This also leads to discussion and deciding on biosafety regulation a very difficult argument.

HAZARDOUS MATERIALS USED IN BIOTECHNOLOGY — HANDLING AND DISPOSAL

(A) Waste Categories

Hazardous waste can be broadly categorised into four categories: Chemical, radioactive, biohazardous and material that is sharp. Each category has hazards which have an effect on safer handling and safe disposal practices, and a specific waste may have properties of more than one category.

Chemical waste: Chemical wastes which are hazardous are disposed through a hazardous waste disposal program managed by the safety department. The term "hazardous" refers to materials or chemicals that are corrosive, flammable, reactive, explosive or toxic. The regulatory description of hazardous waste, in a broader sense, includes the majority of known chemicals when they are to be discarded.

The waste disposal of hazardous chemicals is managed in accordance with regulation of the Cregon Department of Environmental Quality (DEQ) and the U.S. Environmental Protection Agency. These regulations suggest specific methods for disposal of different types of hazardous chemical wastes. Therefore, the safety department has specific guidelines which must be strictly followed with reference to packaging, labelling, and disposal of hazardous waste. Since generators are charged for costs associated with waste disposal, guidelines have also been established by the safety department for recycling and waste minimizing methods.

Radioactive waste: Radioactive substances are most toxic. As compared to organic poisons, infurious effects of radio-nuclides are exceedingly high. For example, radium is 25,000 times more lethal than arsenic. Nuclear war materials, test explosions, craze for power plants, radioisotope use in medicine, industry and research are the main source of radioactive pollution that could threaten our environmental security.

There is no suitable and cheap method of disposal of radioactive waste (spent nuclear fuel gaseous effluents and low level wastes). At any time radioactivity is likely to escape from the waste in water bodies, concrete cases and salt formations in high mountains. The nuclear waste is thus likely to get leached into the biosphere.

Pollution control boards and environmental protection agencies must evolve certain foolproof methods to prevent above mentioned pollution by handling radioactive wastes carefully.

Biohazardous waste: Biological hazard or biohazard means infectious agents causing a risk of death, injury or illness to individuals who handle them. All waste materials which contain such agents must be autoclaved or chemically sterilized before disposing into the general trash. A control *viz.,* sterilizer indicator tape has to be used to assure the effectiveness of treatment. Toxicity and radioactivity like hazards should not be ignored when disposing of sterilized materials. Provided sterlization is not practical, then biohazardous material must be incinerated in a DEQ-permitted infections waste incinerator.

Sharp materials: Sharp materials including needles, broken glass, and razor blades provide danger both to initial users and to others who may come in contact with that. Besides causing physical damage, such materials, when contaminated, can provide an entry route into the body for toxic or infectious substances. Therefore, sharp materials should be enclosed in a rigid container and placed in garbage dumpsters.

(B) Instructions for Hazardous Waste Disposal

Proper disposal of chemical wastes is required by central and state governmental laws. For waste generators three steps are suggested: packaging the waste properly, filling out the chemical collection request and sending the request to Linfield Safety Department. However, there is no charge for the pickup service and department billing for hazardous waste disposal will be only for the materials disposed off as billed by the disposal agency.

(*a*) Packaging the waste: Package the waste in a leak-proof container with a screw-up lid or other secure closer. However, snapcaps (such as those found on milk bottles), wrong size caps, parafilm, or other loose-fitting lids, are not acceptable.

Solid debris can be packaged into sealed plastic bags. Biohazard bags are not to be used for chemically hazardous waste.

(*b*) Fill up the chemical collection request form: The following information has to be filled legibly:

(*i*) Name: Name of the person to be contacted if any questions are to be clarified. He or she should be knowledgeable about the chemical characteristics of the waste and the processes used to generate the waste.

(*ii*) Date: State and federal law allows one to store waste on campus for not more than 90 days. If any container was used to accumulate waste, the date should indicate the last day waste was added.

(*iii*) Department: Departments are charged for waste disposal. Therefore, it has to track who generates a particular area-waste for billing and to help in pollution prevention planning.

(*iv*) Phone details: List the number where the generator can be reached.

(*v*) Building and room. Please mention the building and room where the packed waste product can be located when collectors arrive to pick it up the (not office/corporate office address).

Chemical Contents and Properties

Chemical name and common name: Used as the basic identifiers for the waste product.

Constituents and percentages: List all the constituents in the container, including solvents and water, by full name, not by abbreviation, initials or chemical formula. Mention their approximate proportions, which should add up to 100%. If the proportions are unknown, indicate that the container holds a mixture and identify the components as well as one can.

Properties, Number of Containers, Container type

Follow the check off and blank fill-in to complete these sections (they are self-explanatory):

Quantity per container: Indicate the amount of waste in the container, not the size of the container, using one of the following units of measure: Litre (including ml etc.), gallon, gram (including kg, etc.), pound. For example, two litres of waste in a four-litre container should be entered as two litres.

- **Total quantity:** Amount in all containers.
- **pH:** Measure the pH and indicate.
- **Major hazards:** Be sure to indicate all hazards.
- **Comments:** Add any comments that you feel would be helpful in classification and handling of the material.

The rest of the form will be completed by the Environmental Health and Safety Department representative picking up the material.

Arranging for waste pickup

Send a copy of the completed request to safety department, unit 4002. Attach a copy of the request to the waste container. The concerned agency will pickup the waste within a week of receiving the request.

The marked containers should be left in a visible place in the room noted on the request form.

Problem request forms

While most chemical collection requests the agency receive are usable, there are some common problems that create bad request; further there are some unusually ugly requests. Common mistakes found on requests include:

(*a*) Signing initials or the name of a laboratory in the column designated for the investigator/generator. A responsible person should be available to clarify any questions regarding the waste.

(*b*) Failure to list the building and room where the waste can be located.

(*c*) Failure to identify 100% of the chemical constituents.

(*d*) Failure to identify any of the constituents at all. Disposing of "unknown" chemicals is extremely expensive.

(*e*) Using chemical formulas to identify the chemical constituents in the waste. For clear communication and to comply with the applicable laws, rules and regulations, the names of the chemical constituents must be written out completely.

(*f*) Using trade names, abbreviations, of waste instead of listing waste chemical constituents. Refer to the MSDS for the chemical constituents, or attach a copy of MSDS within the waste.

Hazardous Waste Disposal Guide

(*a*) *Office and shop waste*

Both office and shop settings typically utilize products that are found also in homes. Environmental regulations allow homeowners greater leeway in disposal of materials than in the workplace environment. What people are used to legally throwing away at home may not be legal to do at work.

(*b*) Aerosol-cans

All aerosol cans are considered hazardous waste until completely empty and punctured. Campus departments may purchase devices to open aerosol cans and drain contents, except for cans with pesticides or other highly toxic materials. Cans will be picked up as with other hazardous wastes. Departments which produce a lot of aerosol cans are encouraged to purchase their own opening device, in consultation with the Linfield College Safety Department.

(*c*) *Office-products*

In the past, correction fluid ("white-out"), duplicating fluid, glues, and various thinners for these products were extensively used in offices. With the advent of word processing systems and photocopiers, the use of these solvent-based products has decreased. Containers that are not

completely dry are typically hazardous waste when disposed. In addition, toner fluid (for copiers and printers) may be hazardous, depending on constituents. Inks used for stamp pads or certain pens are typically hazardous.

(*d*) *Cleaning-products*

Many cleaning products have a high or low enough pH to qualify as hazardous waste. Any cleaning product which smells of ammonia is likely to be above the pH allowed for sewer disposal under McMinnville drain disposal regulations. This does not affect the use of these products as intended, but should be kept in mind when getting rid of old or outdated stocks. In addition, many cleaning products contain solvents which may be classified as hazardous waste when disposed.

(*e*) *Rags*

Rags which are to be used for solvent-based purposes should be purchased, when possible, through a laundering service which includes laundering the rags. If this is not feasible, rags with flammable solvents or hazardous constituents should be collected in flammable rag containers and disposed as hazardous waste.

(*f*) *Paint Washers*

Paint washers typically contain flammable or halogenated solvents. Whenever possible, users should set up a recovery system to reclaim the solvent, or arrange for a commercial service which does this. Manufacturers often market replacement solvents which they claim are "non-toxic" or "biodegradable". Their use is encouraged, especially if it results in less chlorinated solvent use. Users must keep in mind, however, that the material they are cleaning may add contaminants to the solvent, such as metals or grease, which make it a hazardous waste.

(*g*) *Paint*

Paint is typically hazardous before drying. The use of lead and mercury in paint has largely disappeared, but the solvents used in both latex and oil-based paints are usually hazardous. Excess unopened or scarcely used paint in good condition should be offered as surplus property. Paint that has been opened should only be thrown away if it is completely dry. If not dry, it can be painted on something or disposed as hazardous waste. There are methods to recycle latex paint to groups that can use it.

Waste Reduction

(*a*) *Waste-costs*

The cost to dispose of hazardous chemical waste will often exceed the original purchase price of a chemical or chemical product. The Linfield College Safety Department encourages waste generators to use waste reduction techniques. If followed, the techniques listed below will help reduce the volume of waste, which will have a corresponding effect on the cost of disposal. Because the costs are variable, they are not listed here. Call the Linfield College Safety Department for current disposal rates.

In addition to disposal costs, there are fines from regulatory agencies for not properly handling waste materials. These fines can be as much as $10,000 per day, and are closely tied into storage and labeling guidelines.

(*b*) *Purchasing*

Purchase chemicals to match anticipated needs. This aspect of waste and cost reduction is frequently overlooked. A substantial portion of hazardous waste generated at Linfield College

consists of chemicals that are in original containers, and are unused or of questionable purity due to previous use. Projected savings from purchasing chemicals in a large size are often offset by costs for disposal of unused portions of larger bottles, especially those with a limited shelf life. It may not be possible to exactly determine future needs, but any effort will be beneficial.

(*c*) *Change-procedures*

A procedure which uses a hazardous substance can often be modified to lessen the hazard or amount of waste products resulting from that procedure. In many cases, a less hazardous material can be substituted and perform as well. An example is substituting a commercial lab glass cleaner (*e.g.*, NOCHROMIX) in place of chromic acid cleaning solution. The resulting mixture is still hazardous because of its corrosive properties, but has no toxic chromium and can therefore be neutralized. Reactive substances those that react with water or air or are unstable are especially troublesome disposal items. Disposal costs associated with picric acid, for example, can be as much as ten times the original purchase price.

(*d*) *Unknowns*

Unknowns are difficult and expensive to dispose. Unknowns can be prevented by good record keeping and labeling, which includes designation of constituents and percentages. If unknowns are found, the responsible department must make every effort to identify the material. If this is not possible, then the responsible department will be billed for the cost of identification or classification required for disposal of the unknown chemical, in addition to disposal costs.

(*e*) *Recycling*

Chemical recycling is possible if material is in unopened containers or partially used original containers and of high quality. These materials are made available to interested parties at Linfield College. Be careful not to obliterate any parts of labels. Chemicals and chemical products should not be given or sold to the general public or offered as surplus property. Commercial chemical products may be offered for surplus if reasonable cautions are followed.

(*f*) *Segregate*

Segregate wastes as much as possible. Mixing a low-cost disposal item with a higher one makes the entire lot a higher-cost item.

(*g*) *Storage*

The storage of hazardous materials must be in compliance with federal and state regulations. Your methods of handling waste are subject to unannounced inspections by state regulatory inspectors.

All containers need to have a label at all time indicating contents. For waste materials, this could be a simple label such as “WASTE SOLVENT” or “USED ACETONE”.

Put the label on the container BEFORE ADDING WASTE.

All containers need a lid at all times when not actively adding or removing waste.

Evaporation in a hood is not a legal disposal method. Funnels do not count as lids.

Secondary containment is advised for liquid containers.

Storage limits and locations are the same for waste as for new materials. For example, storage of flammable liquids in excess of 10 gallons requires a flammable liquid storage cabinet. Glass bottles may not be stored on the floor because they can easily be broken by accidental kicking.

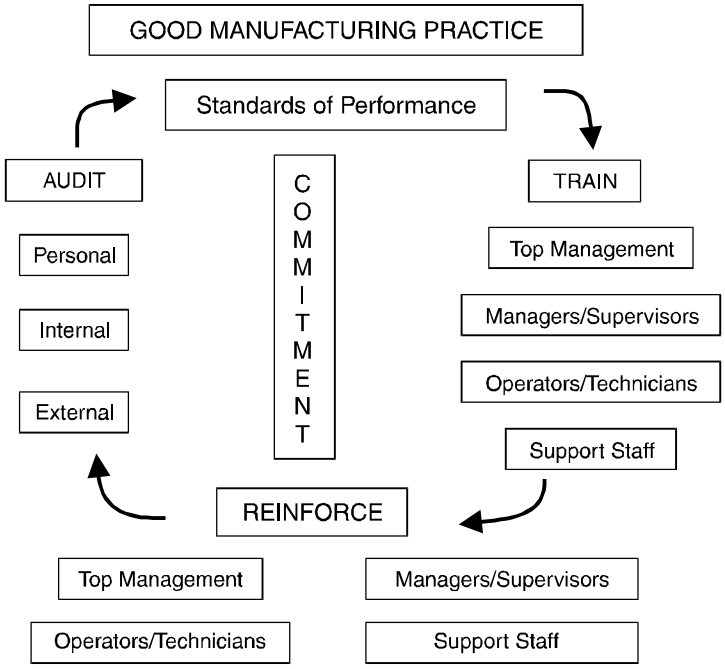
GOOD MANUFACTURING PRACTICES

What is GMP?

GMP refers to the Good Manufacturing Practice regulations promulgated by the US Food and Drug Administration under the authority of the Federal Food, Drug, and Cosmetic Act (FDA).

These regulations, which have the force of law, require that manufacturers, processors, and packagers of drugs, medical devices, some food, and blood take proactive steps to ensure that their products are safe, pure, and effective. GMP regulations require a quality approach to manufacturing, enabling companies to minimize or eliminate instances of contamination, mix-ups, and errors. This in turn, protects the consumer from purchasing a product which is not effective or even dangerous. Failure of firms to comply with GMP regulations can result in very serious consequences including recall, seizure, fines, and jail time.

GMP regulations address issues including recordkeeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling. Most GMP requirements are very general and open-ended, allowing each manufacturer to decide individually how to best implement the necessary controls.



Example of Good Manufacturing Practices

Approved drug manufacturing equipment

The GMPs require that equipment be of appropriate design to facilitate operations for its intended use and for cleaning and maintenance and, that any equipment surface in contact with components, in-process materials, or drug products not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

GOOD LABORATORY PRACTICES (GLP)

During the 1970s, there were several problems which made some scientific reports unreliable. These reports had been submitted to international regulatory authorities and decisions about the safety of materials to man and the environment were made on the basis of this unreliable information.

Consequently the US Government introduced the first **Good Laboratory Practice (GLP)** regulations in 1978. Other countries followed with different GLP standards and the Organisation for Economic Cooperation and Development (OECD) published the worldwide principles of **Good Laboratory Practice in 1981.** Adherence to these OECD standards permits international acceptability of safety testing from different countries.

In the first part we will examine the nature of the problems that caused the introduction of GLP and how the international scientific and regulatory community responded to these problems. We will also discuss how international co-operation in GLP is organised.

GLP is based on sound, common-sense principles. There is nothing required by GLP that exceeds what any conscientious scientist would do when producing quality research and development.

GLP is concerned with how we organise our laboratories and how we organise our studies. It addresses responsibilities for managing the people, facilities and equipment required for good science and how we plan, perform and report our experiments and studies. Most importantly, GLP does not interfere with the ability of scientists to make scientific decisions.

GOOD LABORATORY PRACTICE PRINCIPLES

1. Test Facility Organisation and Personnel

Management's responsibilities

Test facility management should ensure that the principles of good laboratory practice is complied with in the test facility.

2. At minimum it should

(*a*) ensure that qualified personnel, appropriate facilities, equipment, and materials are available;

(*b*) maintain a record of the qualifications, training, experience and job description for each professional and technical individual;

(*c*) ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions;

(*d*) ensure that health and safety precautions are applied according to national and/or international regulations;

(*e*) ensure that appropriate standard operating procedures are established and followed;

(*f*) ensure that there is a Quality Assurance Programme with designated personnel;

(*g*) where appropriate, agree to the study plan in conjunction with the sponsor;

(*h*) ensure that amendments to the study plan are agreed upon and documented;

(*i*) maintain copies of all study plans;

(*j*) maintain a historical file of all Standard Operating Procedures;

(*k*) for each study ensure that a sufficient number of personnel is available for its timely and proper conduct;

(*l*) for each study designate an individual with the appropriate qualifications, training, and experience as the Study Director before the study is initiated. If it is necessary to replace a Study Director during a study, this should be documented;

(*m*) ensure that an individual is identified as responsible for the management of the archives.

Study Director's Responsibilities

1. The Study Director has the responsibility for the overall conduct of the study and for its report.

2. These responsibilities should include, but not be limited to, the following functions:

(*a*) should agree to the study plan;

(*b*) ensure that the procedures specified in the study plan are followed, and that authorization for any modification is obtained and documented together with the reasons for them;

(*c*) ensure that all data generated are fully documented and recorded;

(*d*) sign and date the final report to indicate acceptance of responsibility for the validity of the data and to confirm compliance with these Principles of Good Laboratory Practice;

(*e*) ensure that after termination of the study, the study plan, the final report, raw data and supporting material are transferred to the archives.

Personnel Responsibilities

1. Personnel should exercise safe working practice. Chemicals should be handled with suitable caution until their hazard(s) has been established.

2. Personnel should exercise health precautions to minimise risk to themselves and to ensure the integrity of the study.

3. Personnel known to have a health or medicinal condition that is likely to have an adverse effect on the study should be excluded from operations that may affect the study.

Quality Assurance Programme

General

1. The test facility should have a documented quality assurance programme to ensure that studies performed are in compliance with these Principles of Good Laboratory Practice.

2. The quality assurance programme should be carried out by an individual or by individuals designated by and directly responsible to management and who are familiar with the test procedures.

3. This individual(s) should not be involved in the conduct of study being assured.

4. This individual(s) should report any finding in writing directly to management and to the Study Director.

Responsibilities of the quality assurance personnel

1. The responsibilities of the quality assurance personnel should include, but not be limited to, the following functions:

(*a*) ascertain that the study plan and Standard Operating Procedures are available to personnel conducting the study;

(*b*) ensure that the study plan and Standard Operating Procedures are followed by periodic inspections of the test facility and/or by auditing the study in progress. Records of such procedures should be retained.

(*c*) promptly report to management and the Study Director unauthorised deviations from the study plan and from Standard Operation Procedures;

(*d*) review the final reports to confirm that the methods, procedures, and observations are accurately described, and that the reported results accurately reflect the raw data of the study;

(*e*) prepare and sign a statement, to be included with the final report, which specifies the dates inspections were made and the dates any findings were reported to management and to the Study Director.

3. Facilities

General

1. The test facility should be of suitable size, construction and location to meet the requirements of the study and minimise disturbances that would interfere with the validity of the study.

2. The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of each study.

Test system facilities

1. The test facility should have a sufficient number of rooms or areas to assure the isolation of test systems and the isolation of individual projects, involving substances known or suspected of being biohazardous.

2. Suitable facilities should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of test systems.

3. There should be storage areas as needed for supplies and equipment. Storage areas should be separated from areas housing the test systems and should be adequately protected against infestation and contamination. Refrigeration should be provided for perishable commodities.

Facilities for handling test and reference substances

1. To prevent contamination or mix-ups, there should be separate areas for receipt and storage of the test and reference substances, and mixing of the test substances with a vehicle.

2. Storage areas for the test substances should be separated from areas housing the test systems and should be adequated to preserve identity, concentration, purity, and stability, and ensure safe storage for hazardous substances.

Archive facilities

1. Space should be provided for archives for the storage and retrieval of raw data, reports, samples, and specimens.

Waste disposal

1. Handling and disposal of wastes should be carried out in such a way as not to jeopardise the integrity of studies in progress.

2. The handling and disposal of wastes generated during the performance of a study should be carried out in a manner which is consistent with pertinent regulatory requirements. This would include provision for appropriate collection, storage, and disposal facilities, decontamination and transportation procedures, and the maintenance of records related to the preceding activities.

4. Apparatus, Material, and Reagents

Apparatus

1. Apparatus used for the generation of data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity.

2. Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of procedures should be maintained.

Material

Apparatus and materials used in studies should not interfere with the test systems.

Reagents

Reagents should be labelled, as appropriate, to indicate source, identity, concentration, and stability information and should include the preparation dates, earliest expiration date, specific storage instructions.

5. Test Systems

Physical/Chemical

(*a*) Apparatus used for the generation of physical/chemical data should be suitably located and of appropriate design and adequate capacity.

(*b*) Reference substances should be used to assist in ensuring the integrity of the physical/chemical test systems.

Biological

(*a*) Proper conditions should be established and maintained for the housing, handling and care of animals, plants, microbial as well as other cellular and sub-cellular systems, in order to ensure the quality of the data.

(*b*) In addition, conditions should comply with appropriate national regulatory requirements for the import, collection, care and use of animals, plants, microbial as well as other cellular and sub-cellular systems.

(*c*) Newly-received animal and plant test systems should be isolated until their health status has been evaluated. If any unusual mortality or morbidity occurs, this lot should not be used in studies and, when appropriate, humanely destroyed.

(*d*) Records of source, date of arrival, and arrival condition should be maintained.

(*e*) Animal, plant, microbial, and cellular test systems should be acclimatised to the test environment for an adequate period before a study is initiated.

(*f*) All information needed to properly identify the test systems should appear on their housing or containers.

(*g*) The diagnosis and treatment of any disease before or during a study should be recorded.

6. Test and Reference Substances

Receipt, handling, sampling and storage

(*a*) Records including substance characterisation, date of receipt, quantities received, and used in studies should be maintained.

(*b*) Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability is assured to the degree possible and contamination or mix-up are precluded.

(*c*) Storage container(s) should carry identification information, earliest expiration date, and specific storage instructions.

Characterisation

(*a*) Each test and reference substance should be appropriately identified (*e.g.,* code, chemical abstract number (CAS), name).

(*b*) For each study, the identity, including batch number, purity, composition, concentrations, or other characterisations to appropriately define each batch of the test or reference substances should be known.

(*c*) The stability of test and reference substances under conditions of storage should be known for all studies.

(*d*) The stability of test and reference substances under the test conditions should be known for all studies.

(*e*) If the test substance is administered in a vehicle, Standard Operating Procedures should be established for testing the homogeneity and stability of the test substance in that vehicle.

(*f*) A sample for analytical purposes from each batch of test substance should be retained for studies in which the test substance is tested longer than four weeks.

7. Standard Operating Procedures

General

(*a*) A test facility should have written Standard Operating Procedures approved by management that are intended to ensure the quality and integrity of the data generated in the course of the study.

(*b*) Each separate laboratory unit should have immediately available Standard Operating Procedures relevant to the activities being performed therein. Published textbooks, articles and manuals may be used as supplements to these Standard Operating Procedures.

Application

1. Standard Operating Procedures should be available for, but not limited to, the following categories of laboratory activities. The details given under each heading are to be considered as illustrative examples.

(*a*) Test and Reference Substance.

Receipt, identification, labelling, handling, sampling, and storage.

(*b*) Apparatus and Reagents.

Use, maintenance, cleaning, calibration of measuring apparatus and environmental control equipment; preparation of reagents.

(*c*) Record keeping.

Reporting, Storage and Retrieval Coding of studies, data collection, preparation of reports, indexing systems, handling of data, including the use of computerised data systems.

(*d*) Test system (where appropriate):

(*i*) Room preparation and environmental room conditions for the test system.

(*ii*) Procedures for receipt, transfer, proper placement, characterisation, identification and care of test system.

(*iii*) Test system preparation, observations examinations, before, during and at termination of the study.

(*iv*) Handling of test system individuals found moribund or dead during the study.

(*v*) Collection, identification and handling of specimens including necropsy and histopathology.

(*e*) Quality Assurance Procedures.

Operation of quality assurance personnel in performing and reporting study audits, inspections, and final study report reviews.

(*f*) Health and Safety Precautions.

As required by national and/or international legislation or guidelines.

8. Performance of the Study

Study plan

1. For each study, a plan should exist in a written form prior to initiation of the study.

2. The study plan should be retained as raw data.

3. All changes, modifications, or revisions of the study plan, as agreed to by the Study Director, including justification(s), should be documented, signed and dated by the Study Directors, and maintained with the study plan.

Content of the study plan

The study plan should contain, but not be limited to the following information:

1. Identification of the Study, the Test and Reference Substances

(*a*) A descriptive title;

(*b*) A statement which reveals the nature and purpose of the study;

(*c*) Identification of the test substance by code or name (IUPAC; CAS number, etc.);

(*d*) The reference substance to be used.

2. Information Concerning the Sponsor and the Test Facility

(*a*) Name and address of the Sponsor;

(*b*) Name and address of the Test Facility;

(*c*) Name and address of the Study Director.

3. Dates

(*a*) The date of agreement to the study plan by signature of the Study Director, and when appropriate, of the sponsor and/or the test facility management;

(*b*) The proposed starting and completion dates.

4. Test Methods

Reference to OECD Test Guideline or other test guideline to be used.

5. Issues (where applicable)

(*a*) The justification for selection of the test system;

(*b*) Characterisation of the test system, such as the species, strain, sub-strain, source of supply, number, body weight range, sex, age, and other pertinent information;

(*c*) The method of administration and the reason for its choice;

(*d*) The dose levels and/or concentration(s), frequency, duration of administration;

(*e*) Detailed information on the experimental design, including a description of the chrono-

logical procedure of the study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed.

6. Records

A list of records to be retained.

Conduct of the study

1. A unique identification should be given to each study. All items concerning this study should carry this identification.

2. The study should be conducted in accordance with the study plan.

3. All data generated during the conduct of the study should be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries should be signed or initialled and dated.

4. Any change in the raw data should be made so as not to obscure the previous entry, and should indicate the reason, if necessary, for change and should be identified by date and signed by the individual making the change.

5. Data generated as a direct computer input should be identified at the time of data input by the individual(s) responsible for direct data entries. Corrections should be entered separately by the reason for change, with the date and the identity of the individual making the change.

9. Reporting of Study Results

General

1. A final report should be prepared for the study.

2. The use of the International System of Units (SI) is recommended.

3. The final report should be signed and dated by the Study Director.

4. If reports of principal scientists from co-operating disciplines are included in the final report, they should sign and date them.

5. Corrections and additions to a final report should be in the form of an amendment. The amendment should clearly specify the reason for the corrections or additions and should be signed and dated by the Study Director and by the principal scientist from each discipline involved.

Content of the final report

The final report should include, but not be limited to, the following information:

1. Identification of the Study, the Test and Reference Substance

(*a*) A descriptive title;

(*b*) Identification of the test substance by code or name (IUPAC; CAS number, etc.);

(*c*) Identification of the reference substance by chemical name;

(*d*) Characterisation of the test substance including purity, stability and homogeneity.

2. Information Concerning the Test Facility

(*a*) Name and address;

(*b*) Name of the Study Director;

(*c*) Name of other principal personnel having contributed reports to the final report.

3. Dates

(*a*) Dates on which the study was initiated and completed.

4. Statement

(*a*) A Quality Assurance statement certifying the dates inspections were made and the dates any findings were reported to management and to the Study Director.

5. Description of Materials and Test Methods

(*a*) Description of methods and materials used;

(*b*) Reference to OECD Test Guidelines or other test guidelines.

6. Results

(*a*) A summary of results;

(*b*) All information and data required in the study plan;

(*c*) A presentation of the results, including calculations and statistical methods;

(*d*) An evaluation and discussion of the results and, where appropriate, conclusions.

7. Storage

The location where all samples, specimens, raw data, and the final report are to be stored.

10. Storage and Retention of Records and Material

Storage and retrieval

1. Archives should be designed and equipped for the accommodation and the secure storage of:

(*a*) the study plans;

(*b*) the raw data;

(*c*) the final reports;

(*d*) the reports of laboratory inspections and study audits performed according to the Quality Assurance Programme;

(*e*) samples and specimens.

2. Material retained in the archives should be indexed so as to facilitate orderly storage and rapid retrieval.

3. Only personnel authorised by management should have access to the archives. Movement of material in and out of the archives should be properly recorded.

Retention

1. The following should be retained for the period specified by the appropriate authorities:
(*a*) The study plan, raw data, samples, specimens, and the final report of each study

(*b*) Records of all inspections and audits performed by the Quality Assurance Programme

(*c*) Summary of qualifications, training, experience and job description of personnel

(*d*) Records and reports of the maintenance and calibration of equipment

(*e*) The historical file of Standard Operating Procedures

2. Samples and specimens should be retained only as long as the quality of preparation permits evaluation.

3. If a test facility or an archive contracting facility goes out of business and has no legal successor, the archive should be transferred to the archives of the sponsor(s) of the study(s).

Unit 2: Intellectual Property Rights

Intellectual property, often known as IP, allows people to own their creativity and innovation in the same way that they can own physical property. The owner of IP can control and be rewarded for its use, and this encourages further innovation and creativity to the benefit of us all.

In some cases, IP gives rise to protection for ideas but in other areas, there will have to be more elaboration of an idea before protection can arise. It will often not be possible to protect IP and gain IP rights (or IPRs) unless, they have been applied for and granted, but some IP protection such as copyright arises automatically, without any registration, as soon as there is a record in some form of what has been created.

The four main types of IP are:

- Patents for inventions—new and improved products and processes that are capable of industrial application
- Trade marks for brand identity—of goods and services allowing distinctions to be made between different traders
- Designs for product appearance—of the whole or a part of a product resulting from the features of, in particular, the lines, contours, colours, shape, texture or materials of the product itself or its ornamentation
- Copyright for material—literary and artistic material, music, films, sound recordings and broadcasts, including software and multimedia.

However, IP is much broader than this extending to trade secrets, plant varieties, geographical indications, performers rights and so on. To understand exactly what can be protected by IP, you will need to check the four main areas of copyright, designs, patents and trade marks as well as other IP. Often, more than one type of IP may apply to the same creation.

Patent

A patent gives an inventor the right for a limited period to stop others from making, using or selling an invention without the permission of the inventor. It is a deal between an inventor and the state in which the inventor is allowed a short-term monopoly in return for allowing the invention to be made public.

Patents are about functional and technical aspects of products and processes. Most patents are for incremental improvements in known technology—evolution rather than revolution. The technology does not have to be complex.

- Specific conditions must be fulfilled to get a patent. Major ones are that the invention must be new. The invention must not form part of the "state of the art". The state of the art is everything that has been made available to the public before the date of applying for the patent. This includes published documents and articles, but can also include use,

display, spoken description, or any other way in which information is made available to the public.

- Involve an inventive step, as well as being new, the invention must not be obvious from the state of the art. Obviousness is from the viewpoint of a person skilled in the area of technology that the invention is in.
- Be industrially applicable. This condition requires that the invention can be made or used in any kind of industry.

A patented invention is recorded in a patent document. A patent document must have

- description of the invention, possibly with drawings, with enough details for a person skilled in the area of technology to perform the invention.
- claims to define the scope of the protection. The description is taken into account while interpreting the claims.

The original patent document of a patent application is published by a patent office. The application then adds to the state of the art for later applications and anyone can comment on the application. Often the patent document needs altering or amending to meet the conditions above before a patent can be granted. The final version of the granted patent document is then republished. If more information about the state of the art is discovered after grant, the patent document can be amended and republished again.

Patent rights are territorial; a UK patent does not give rights outside of the UK. Patent rights last for up to 20 years in the UK. Some patents, such as those for medicinal products, may be eligible for a further 5 years protection with a Supplementary Protection Certificate.

A patent can be of value to an inventor—as well as protecting his business, patents can be bought, sold, mortgaged, or licenced to others. They also benefit people other than the inventor since large amounts of information can be learnt from other peoples patents — they can stop you from reinventing things or you can monitor what your competitors are doing. Patents also spur you or others on to develop your idea further, and once the term of the patent expires it can be freely performed by anyone which benefits the public and the economy.

TRADEMARK

A trademark is any sign which can distinguish the goods and services of one trader from those of another. A sign includes words, logos, colours, slogans, three-dimensional shapes and sometimes sounds and gestures. A trademark is therefore a "badge" of trade origin. It is used as a marketing tool so that customers can recognize the product of a particular trader. To be registrable in the UK it must also be capable of being represented graphically, that is, in words and/or pictures.

DESIGN

A design refers to the appearance of the whole or a part of a product resulting from the features of, in particular, the lines, contours, colours, shape, texture or materials of the product or its ornamentation.

In the United Kingdom, designs are protected by three legal rights:

(*a*) Registered designs rights

- gives the owner a monopoly on their product design.
- brings the right to take legal action against others who might be infringing the design and to claim damages.

- may deter a potential infringement.
- also brings the exclusive right to make, offer, put on the market import, export, use or stock any product to which the design has been applied or is incorporated or to let others use the design under the terms agreed with the registered owner, in the UK and the Isle of Man.

Design registration gives the owner a monopoly on their product design, *i.e.*, the right for a limited period to stop others from making, using or selling a product to which the design has been applied, or in which it has been incorporated without their permission and is additional to any design right or copyright protection that may exist automatically in the design.

(*b*) Unregistered design right.

Is not a monopoly right but a right to prevent deliberate copying, and lasts until 10 years after first marketing articles made to the design, subject to an overall limit of 15 years from creation of the design. Unlike design registration, you do not have to apply to register design right. A design right is a property that, like any other business commodity, may be bought, sold or licensed.

(*c*) Artistic copyright.

Work can only be original if it is the result of independent creative effort. It will not be original if it has been copied from something that already exists. If it is similar to something that already exists but there has been no copying from the existing work either directly or indirectly, then it may be original.

The term "original" also involves a test of substantiality—literary, dramatic, musical and artistic works will not be original if there has not been sufficient skill and labour expended in their creation. But, sometimes significant investment of resources without significant intellectual input can still count as sufficient skill and labour.

Ultimately, only the courts can decide whether something is original, but there is much case law indicating, for example, that names and titles do not have sufficient substantiality to be original and that, where an existing work is widely known, it will be difficult to convince a court that there has been no copying if your work is very similar or identical.

Sound recordings, films and published editions do not have to be original but they will not be new copyright works if they have been copied from existing sound recordings, films and published editions.

Broadcasts do not have to be original, but there will be no copyright, if, or to the extent that, they infringe copyright in another broadcast.

IMPLICATIONS OF IPRs AND AGRICULTURAL TECHNOLOGY

The dynamics and interplay of IPRs and technological innovations have multiple impacts. These can be categorized into social, economic and ecological. Due to peculiarities of Indian agriculture, the magnitude of these impacts will be manifold. The IPR regime not only influences research portfolio but also the contours of technology development. Primarily, the underlying motive of protection is to share profits with innovators. Therefore, the economic implications are not only predominant but also most obvious. The other two implications of access to newer technologies are on social and ecological dimensions. These three impacts are not mutually exclusive and often overlap.

Social Implications

Social impact of new technologies is manifested in terms of its influence on equity. Other

important issue pertains to "scale effect". These issues can be explained by the illustration of Green Revolution. This seed-fertiliser technology was predominantly applicable in the areas with assured irrigation. These technologies contributed to the widening of the regional disparity. Viewed from a macro-perspective, however, the revolution was a great success that helped realize cherished goal of self-sufficiency in food grains. Therefore, the magnitude and nature of social implications vary according to the category of the technology (Table). Knowledge-based technologies and technologies concerning conservation of natural resources have positive impact on the society. Because of their nature (public good), the net social welfare increases manifold. Certain technologies like HYVs and hybrids require intensive input use and therefore have a mixed impact on the society. The predominant positive impact (+ + –) clouds the negative effects. Yield enhancement by conventional breeding is an ideal example.

By the same yardstick, if conventional breeding aims at preventing yield loss (pest- and disease-resistant varieties) it becomes cost-reducing and has no negative impact (+). There are technologies where the negative component impact is marked (– +). Current levels of technologies (and its costs) in farm machinery and power precludes their accessibility to small and marginal farmers. There is a distinct possibility that in the near future farm machinery is tailor-made to suit small holdings ?

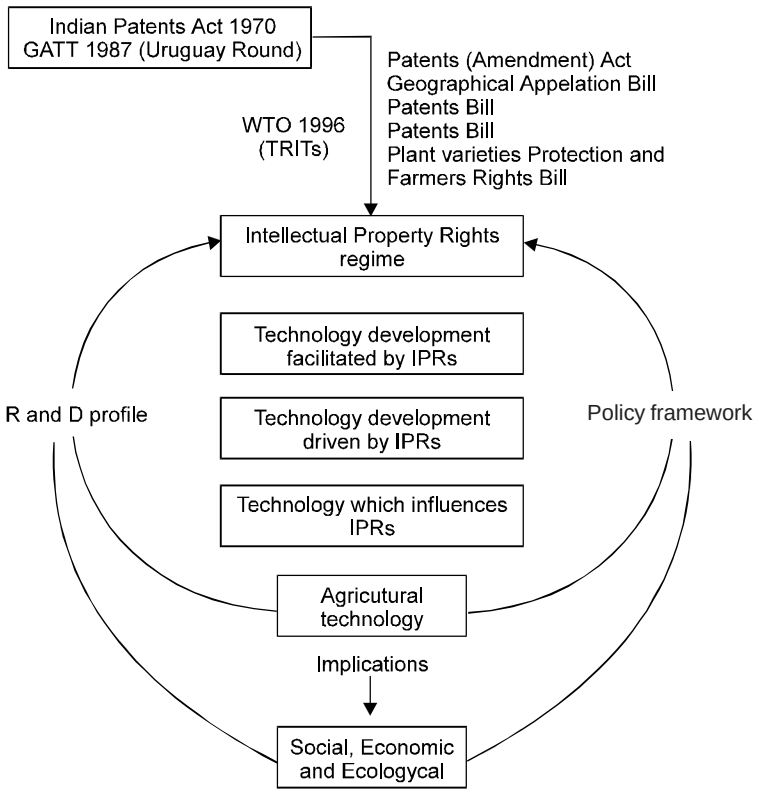


Fig. 2.1. Chemicals used in agriculture.

Economic Implications

Most technologies, excluding agricultural biotechnology and crop protection chemicals have a net positive impact on the economy. There are also implicit benefits like savings from poten-

tial losses due to pests and diseases. Newer techniques invariably shift production functions thereby improving income of individuals and that of the nation. Research in the public domain will concentrate in cost-reducing technologies that are helpful to the weaker sections. Conservation of genetic resources have huge positive externalities (both intra and inter generational). Considering the market structure of crop varieties and crop protection chemicals and the nature of potential technologies, the scope for market malpractice such as monopoly and cartelisation is real. Generally embodied technologies are likely to have relatively more apparent impacts. Active presence of the public sector is vital for the provision of disembodied technologies.

Ecological implications

Increased use of agrochemicals will accelerate environmental degradation (– – –).Though biotechnological innovations minimise the use of agrochemicals to some extent (+ –), they are feared for their contribution to gene pollution (– ? ?). Development of such resistant varieties by conventional breeding has no negative impacts (++). Any technology encouraging the use of improved varieties is likely to contribute to narrowing of genetic base (–).

Increasingly, the use of antibiotics, hormones, unconventional feeds and genetic engineering in livestock and fisheries have raised questions about health hazards and animal biodiversity (– –). Destruction of soil structure and groundwater depletion are serious ecological risks associated with the excessive use of technologies associated with farm machinery and power. Technological advancements in the conservation of soil, water and genetic resources have profound positive impacts on the ecology (+++). Being locally evolved and practice based, knowledge based technologies optimise resource use thereby imparting positive externalities to the environment.

WORLD TRADE ORGANISATION (WTO)

In brief, the World Trade Organisation (WTO) is the only international organisation dealing with the global rules of trade between nations. Its main function is to ensure that trade flows as smoothly, predictably and freely as possible.

Location: Geneva, Switzerland

Established: 1 January 1995

Created by: Uruguay Round negotiations (1986-94)

Membership: 146 countries (as of April 2003)

Budget: 155 million Swiss francs for 2003

Secretariat staff: 560

Head: Director-General, Supachai Panitchpakdi

Functions:

- Administering WTO trade agreements
- Forum for trade negotiations
- Handling trade disputes
- Monitoring national trade policies
- Technical assistance and training for developing countries
- Cooperation with other international organizations

The result is assurance. Consumers and producers know that they can enjoy secure supplies and greater choice of the finished products, components, raw materials and services that they use. Producers and exporters know that foreign markets will remain open to them. The result is also a more prosperous, peaceful and accountable economic world. Decisions in the WTO are typically taken by consensus among all member countries and they are ratified by members' parliaments. Trade friction is channeled into the WTO's dispute settlement process where the focus is on interpreting agreements and commitments, and how to ensure that countries' trade policies confirm with them. That way, the risk of disputes spilling over into political or military conflict is reduced. By lowering trade barriers, the WTO's system also breaks down other barriers between peoples and nations.

At the heart of the system—known as the multilateral trading system—are the WTO's agreements, negotiated and signed by a large majority of the world's trading nations, and gratified in their parliaments. These agreements are the legal ground-rules for international commerce. Essentially, they are contracts, guaranteeing member countries important trade rights. They also bind governments to keep their trade policies within agreed limits to everybody's benefit. The agreements are negotiated and signed by governments. But their purpose is to help producers of goods and services, exporters, and importers conduct their business. **The goal** is to improve the welfare of the people of the member countries.

A Closer Look at These Principles

1. *Trade without Discrimination*

(*a*) Most-favoured-nation (MFN): Treating other people equally. Under the WTO agreements, countries cannot normally discriminate between their trading partners. Grant someone a special favour (such as a lower customs duty rate for one of their products) and you have to do the same for all other WTO members. This principle is known as Most-Favoured-Nation (MFN) treatment. It is so important that it is the first article of the General Agreement on Tariffs and Trade (GATT), which governs trade in goods. MFN is also a priority in the General Agreement on Trade in Services (GATS) and the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), although in each agreement the principle is handled slightly differently. Together, these three agreement cover all the three main areas of trade handled by the WTO.

Some exceptions are allowed. For example, countries can set up a free-trade agreement that applies only to goods traded within the group—discriminating against goods from outside. Or they can give developing countries special access to their markets. Or a country can raise barriers against products that are considered to be traded unfairly from specific countries. And in services, countries are allowed, in limited circumstances, to discriminate. But the agreements permit these exceptions only under strict conditions. In general, MFN means that every time a country lowers a trade barrier or opens up a market, it has to do so for the same goods or services from all its trading partners—whether rich or poor, weak or strong.

(*b*) National treatment: Treating foreigners and locals equally. Imported and locally-produced goods should be treated equally—at least after the foreign goods have entered the market. The same should apply to foreign and domestic services, and to foreign and local trademarks, copyrights and patents. This principle of "national treatment" (giving others the same treatment as one's own nationals) is also found in all the three main WTO agreements (Article 3 of GATT, Article 17 of GATS and Article of 3 TRIPS), although once again the principle is handled slightly differently in each of these.

National treatment only applies once a product, service or item of intellectual property

has entered the market. Therefore, charging customs duty on an import is not a violation of national treatment even if locally-produced products are not charged an equivalent tax.

2. *Free Trade: Gradually, Through Negotiation*

Lowering trade barriers is one of the most obvious means of encouraging trade. The barriers concerned include customs duties (or tariffs) and measures such as import bans or quotas that restrict quantities selectively. From time to time other issues such as red tape and exchange rate policies have also been discussed.

Since GATT's creation in 1947-48 there have been eight rounds of trade negotiations. A ninth round, under the Doha Development Agenda, is now underway. At first, these are focused on lowering tariffs (customs duties) on imported goods. As a result of the negotiations, by the mid-1990s industrial countries' tariff rates on industrial goods had fallen steadily to less than 4%.

But by the 1980s, the negotiations had expanded to cover non-tariff barriers on goods, and to the new areas such as services and intellectual property.

Opening markets can be beneficial, but it also requires adjustment. The WTO agreements allow countries to introduce changes gradually, through "progressive liberalization". Developing countries are usually given longer time period to fulfil their obligations.

3. *Predictability: Through Binding and Transparency*

Sometimes, promising not to raise a trade barrier can be as important as lowering one, because the promise gives business a clearer view of their future opportunities. With stability and predictability, investment is encouraged, jobs are created and consumers can fully enjoy the benefits of competition—choice and lower prices. The multilateral trading system is an attempt to governments to make the business environment stable and predictable.

Table 2.1. The Uruguay Round increased bindings. Percentages of tariffs bound before and after the 1986–94 talks

	Before	*After*
Developed countries	78	99
Developing countries	21	73
Transition economies	73	98

(These are tariff lines, so percentages are not weighted according to trade volume or value)

In the WTO, when countries agree to open their markets for goods or services, they "bind" their commitments. For goods, these bindings amount to ceilings on customs tariff rates. Sometimes countries tax imports at rates that are lower than the bound rates. Frequently, this is the case in developing countries. In developed countries, the rates actually charged and the bound rates tend to be the same.

A country can change its bindings, but only after negotiating with its trading partners, which could mean compensating them for loss of trade. One of the achievements of the Uruguay Round of multilateral trade talks was to increase the amount of trade under binding commitments (see Table 2.1). In agriculture, 100% of products now have bound tariffs. The result of all this: a substantially higher degree of market security for traders and investors.

The system tries to improve predictability and stability in other ways as well. One way is to discourage the use of quotas and other measures used to set limits on quantities of imports—

administering quotas can lead to more red-tape and accusations of unfair play. Another is to make countries' trade rules as clear and public (transparent) as possible. Many WTO agreements require governments to disclose their policies and practices publicly within the country or by notifying the WTO. The regular surveillance of national trade policies through the Trade Policy Review Mechanism provides a further means of encouraging transparency both domestically and at the multilateral level.

4. *Promoting Fair Competition*

The WTO is sometimes described as a "free trade" institution, but that is not entirely accurate. The system does allow tariffs and, in limited circumstances, other forms of protection. More accurately, it is a system of rules dedicated to open, fair and undistorted competition.

The rules on non-discrimination—MFN and national treatment – are designed to secure fair conditions of trade. So too are those on dumping (exporting at below cost to gain market share) and subsidies. The issues are complex, and the rules try to establish what is fair or unfair, and how governments can respond, in particular by charging additional import duties calculated to compensate for damage caused by unfair trade.

Many of the other WTO agreements aim to support fair competition: in agriculture, intellectual property, services, for example. The agreement on government procurement (a "plurilateral" agreement because it is signed by only a few WTO members) extends competition rules to purchases by thousands of government entities in many countries, and so on.

5. *Encouraging Development and Economic Reform*

The WTO system contributes to development. On the other hand, developing countries need flexibility in the time they take to implement the system's agreements. And the agreements themselves inherit the earlier provisions of GATT that allow for special assistance and trade concessions for developing countries.

Over three quarters of WTO members are developing countries and countries in transition to market economies. During the seven and a half years of the Uruguay Round, over 60 of these countries implemented trade liberalization programmes autonomously. At the same time, developing countries and transition economies were much more active and influential in the Uruguay Round negotiations than in any previous round, and they are even more, so in the current Doha Development Agenda.

At the end of the Uruguay Round, developing countries were prepared to take on most of the obligations that are required of developed countries. But the agreements did give them transition periods to adjust to the more unfamiliar and, perhaps, difficult WTO provisions—particularly so for the poorest, "least-developed" countries. A ministerial decision adopted at the end of the round says better-off countries should accelerate implementing market access commitments on goods exported by the least-developed countries, and it seeks increased technical assistance for them. More recently, developed countries have started to allow duty-free and quota-free imports for almost all products from least-developed countries. On all of this, the WTO and its members are still going through a learning process. The current Doha Development Agenda includes developing countries' concern about the difficulties they face in implementing the Uruguay Round agreements.

WTO AGREEMENTS

How can you ensure that trade is as fair as possible, and as free as is practical? By negotiating rules and abiding by them.

The WTO's rules—the agreements—are the result of negotiations between the members.

The current set were the outcome of the 1986-94 Uruguay Round negotiations, which included a major revision of the original General Agreement on Tariffs and Trade (GATT). GATT is now the WTO's principal rule-book for trade in goods. The Uruguay Round also created new rules for dealing with trade in services, relevant aspects of intellectual property, dispute settlement, and trade policy reviews. The complete set runs to some 30,000 pages consisting of about 60 agreements and separate commitments (called schedules) made by individual members in specific areas such as lower customs duty rates and services market-opening.

Through these agreements, WTO members operate a non-discriminatory trading system that spells out their rights and their obligations. Each country receives guarantees that its exports will be treated fairly and consistently in other countries' markets. Each promises to do the same for imports into its own market. The system also gives developing countries some flexibility in implementing their commitments.

Goods

It all began with trade in goods. From 1947 to 1994, GATT was the forum for negotiating lower customs duty rates and other trade barriers; the text of the General Agreement spelt out important rules, particularly non-discrimination. Since 1995, the updated GATT has become the WTO's umbrella agreement for trade in goods. It has annexes dealing with specific sectors such as agriculture and textiles, and with specific issues such as state trading, product standards, subsidies and actions taken against dumping.

Services

Banks, insurance firms, telecommunications companies, tour operators, hotel chains and transport companies looking to do business abroad can now enjoy the same principles of freer and fairer trade that originally only applied to trade in goods.

These principles appear in the new General Agreement on Trade in Services (GATS). WTO members have also made individual commitments under GATS stating which of their services sectors they are willing to open to foreign competition, and how open those markets are.

Intellectual Property

The WTO's intellectual property agreement amounts to rules for trade and investment in ideas and creativity. The rules state how copyrights, patents, trademarks, geographical names used to identify products, industrial designs, integrated circuit layout-designs and undisclosed information such as trade secrete–"intellectual property"–should be protected when trade is involved.

Dispute Settlement

The WTO's procedure for resolving trade quarrels under the Dispute Settlement Understanding is vital for enforcing the rules and therefore for ensuring that trade flows smoothly. Countries bring disputes to the WTO if they think their rights under the agreements are being infringed. Judgements by specially-appointed independent experts are based on interpretations of the agreements and individual countries' commitments. The system encourages countries to settle their differences through consultation. Failing that, they can follow a carefully mapped out, stage-by-stage procedure that includes the possibility of a ruling by a panel of experts, and the chance to appeal the ruling on legal grounds. Confidence in the system is borne out by the number of cases brought to the WTO—around 300 cases in eight years compared to the 300 disputes dealt with during the entire life of GATT (1947-94).

Policy Review

The Trade Policy Review Mechanism's purpose is to improve transparency, to create a greater understanding of the policies that countries are adopting, and to assess their impact. Many members also see the reviews as constructive feedback on their policies.

All WTO members must undergo periodic scrutiny, each review containing reports by the country concerned and the WTO Secretariat.

DEVELOPING COUNTRIES DEVELOPMENT AND TRADE

Over three quarters of WTO members are developing or least-developed countries. All WTO agreements contain special provision for them, including longer time periods to implement agreement and commitments, measures to increase their trading opportunities, provisions requiring all WTO members to safeguard their trade interests, and support to help them build the infrastructure for WTO work, handle disputes, and implement technical standards.

The 2001 Ministerial Conference in Doha set out tasks, including negotiations, for a wide range of issues concerning developing countries. Some people call the new negotiations the Doha Development Round.

Before that part in 1997, a high-level meeting on trade initiatives and technical assistance for least-developed countries resulted in an "integrated framework" involving six intergovernmental agencies, to help least-developed countries increase their ability to trade, and some additional preferential market access agreements.

A WTO committee on trade and development, assisted by a sub-committee on least-developed countries, looks at developing countries' special needs. Its responsibility includes implementation of the agreements, technical cooperation, and the increased participation of developing countries in the global trading system.

TECHNICAL ASSISTANCE AND TRAINING

The WTO organizes around 100 technical cooperation missions to developing countries annually. It holds on average three-trade policy courses each year in Geneva for government officials. Regional seminars are held regularly in all regions of the world with a special emphasis on African countries. Training courses are also organized in Geneva for officials from countries in transition from central planning to market economies. The WTO set up reference centres in over 100 trade ministries and regional organizations in capitals of developing and least-developed countries, providing computers and internet-access to enable ministry officials to keep abreast of events in the WTO in Geneva through online access to the WTO's immense database of official documents and other material.

- Assisting developing countries in trade policy issues, through technical assistance and training programmes.
- Cooperating with other international organizations.

THE ORGANIZATION FUNCTIONS

The WTO's overriding objective is to help trade flow smoothly, freely, fairly and predictably. It does this by:

- administering trade agreements;
- acting as a forum for trade negotiations;
- settling trade disputes;
- reviewing national trade policies.

STRUCTURE

The WTO has nearly 150 members, accounting for over 97% of world trade. Around 30 others are negotiating membership. Decisions are made by the entire membership. This is typically by consensus. A majority vote is also possible but it has never been used in the WTO, and was extremely rare under the WTO's predecessor, GATT. The WTO's agreements have been ratified in all members' parliaments.

The WTO's top level decision-making body is the **Ministerial Conference** which meets at least once every two years. The Fifth WTO Ministerial Conference was held in Cancun, Mexico from 10 to 14 September, 2003.

Below this is the **General Council** (normally ambassadors and heads of delegation in Geneva, but sometimes officials sent from members' capitals) which meets several times a year in the Geneva headquarters. The General Council also meets as the Trade Policy Review Body and the Dispute Settlement Body.

At the next level, the **Goods Council, Services Council and Intellectual Property (TRIPS) Council** report to the General Council. Numerous **specialized committees, working groups and working parties** deal with the individual agreements and other areas such as environment, development, membership applications and regional trade agreements.

SECRETARIAT

The WTO Secretariat, based in Geneva has around 560 staff and is headed by a director general. It does not have branch offices outside Geneva. Since decisions are taken by the members themselves, the Secretariat does not have the decision-making role those other international bureaucracies are given.

The secretariat's main duties are to supply technical support for the various councils and committees and the ministerial conferences, to provide technical assistance for developing countries, to analyze world trade, and to explain WTO affairs to the public and media. The Secretariat also provides some forms of legal assistance in the dispute settlement process and advises governments wishing to become members of the WTO. The annual budget is roughly 155 million Swiss francs.

GENERAL AGREEMENT ON TARIFFS AND TRADE (GATT)

The General Agreement on Tariffs and Trade (GATT) was created in 1947. GATT is an agreement between many nations, governing international trade. GATT provides a place for negotiating trade issues and a framework for guiding the conduct of trade. Current GATT membership includes 123 nations. One of the major beliefs behind GATT is that more liberalized trade would help the economies of participating nations grow (Banks 35). Some other principles of GATT are nondiscrimination; what is meant by nondiscrimination is that no member of GATT can discriminate against other nations or who favoritism or give any special privileges to any nations. This allows all trading partners to be put on an equal basis. A second principle, tariff protection, favors the use of tariffs as a clear way to protect domestic industries, as opposed to no tariff measures such as import quotas. A third and final principle behind GATT is providing a stable basis for trade. This is achieved by binding all participating nations to agree upon tariff levels by listing in "tariff schedules" the negotiated tariffs for each country's products (Banks 35).

There has been eight conferences, referred to as rounds or cycles of GATT, each of these rounds resulted in new trade agreements. The most recent round is referred to as the Uruguay

Round because it was launched at a conference in Punte del Este, Uruguay in 1986. These negotiations concluded with the signing by more than 100 of the Uruguay Round "Final Act" in Marrakesh, Morocco in April 1994. The Uruguay Round Agreement has been described as the largest, most comprehensive trade pact in history (Congressional Digest).

The United States had a number of objectives in entering into the Uruguay Round of trade negotiations. These included broadening procedures relating to trade in agricultural products, extending GATT rules to trade in services never before covered by GATT, increasing protection for patents, copyrights, and trademarks, and an improved way for settling disputes among GATT participants. Most of the objectives that the United States brought to the Uruguay Round were achieved. GATT was expanded to include services and new areas relating to the protection of patents and foreign investment. The Uruguay Round also cut tariffs worldwide by about one third; coverage for agriculture, textiles, and clothing was increased. And a new World Trade Organization was created to administer the agreement, oversee dispute settlements, and review countries' trade policies and practices (C.D.).

Nations signing the agreement must have it approved by their governments before they can be subjected to its terms. In the U.S. Congress, consideration for the agreement is taking place under "fast track" procedure, meaning that the House and the Senate must vote up or down on the legislation dealing with the agreement, with no opportunity to introduce or consider amendments. Opponents are concerned that the United States may lose more than it gains. They fear that the World Trade Organization poses a threat to U.S. sovereignty in that the United States may be forced to lower its environmental, health, and safety standards to conform to global rules. An example of this is that a Geneva based trade panel ruled that the U.S. government must halt its boycott of tuna caught with fishing methods that kill large numbers of dolphins (821). The reason that something like this can happen is that nations involved in the GATT are subject to challenges of this sort as illegal trade barriers. The World Trade Organization could also undermine food safety laws by forcing the United States to either accept food with dangerous pesticide levels or pay a substantial fee. They also argue that new taxes may be needed to offset the loss in tariff revenue. Another concern is that U.S. measures to prevent dumping or selling of a product in a foreign market at a price lower than its fair market value could be weakened. But what the opponents of the World Trade Organization fail to realize is that if the Congress passes the Uruguay Round the U.S. will have a much larger say in environmental and food safety standards and the restriction of dumping.

Members of Congress who support the agreement believe that it will bring far reaching economic benefits to the United States, including new employment opportunities and high paying jobs associated with the increased production of goods and services for export (Banks 35). Supporters also feel that import growth resulting from the agreement will keep prices low and broaden consumer choices. A specific group of Americans that will benefit greatly from the passage to GATT in Congress are the farmers. The United States is by far the most efficient farming country with more prime cropland per capita than any other country in the world. Last year U.S. farm exports totaled 42.6 billion dollars which is lower than their 1981 peak. The main reason for this has been the increase of Europe's heavily subsidized farmers (Banks 35). Using 1992 numbers, every one hundred dollars of Europe's farm exports carried an average twenty five dollar subsidy versus one dollar for the United States (Banks 35). If GATT was to pass the gap wouldn't disappear but it would shrink significantly.

Another positive aspect of GATT is that it will open up traditionally closed foreign markets. For example, the U.S. will import three percent of its peanuts and Japan will import at least some of its rice and citrus products, Korea will import some almonds, and so on with other

countries. As a positive look to the future for farmers penetrating foreign markets a study shows that Asians eat on average 11 grams of protein a day compared to 52 for Japanese and 72 for Americans. As the Asian countries' standard of living increases the study says so will their protein intake.

With GATT in place, the likelihood is that an increasing amount of it will be American grown. GATT will cost the United States Treasury about fourteen billion dollars over the next five years in revenues lost because of reduced tariffs. Under budget rules, this tax cut for consumers must be paid for with fourteen billion dollars in increased revenues or decreased spending. Republicans feel that the government already has too much money so they are opposed to new taxes. And the Democrats feel that the government could never have too much money to work with so they oppose spending cuts.

GATT is not perfect but I feel that it would be devastating to allow these different outlooks to impede a trade package that may enlarge the U.S. GDP by a cumulative one trillion dollars over the first ten years (76). GATT will increase U.S. competitiveness in foreign markets and create a great number of high paid, highly-skilled jobs for Americans. Because of these positive factors and small speculative risks I feel that the General Agreement on Tariffs and Trade should be supported by all Americans with great enthusiasm towards the economic future of our nation.

The World Intellectual Property Organization (WIPO) is an international organization dedicated to promoting the use and protection of works of the human spirit. These works—intellectual property—are expanding the bounds of science and technology and enriching the world of the arts. Through its work, WIPO plays an important role enhancing the quality and enjoyment of life, as well as creating real wealth for nations. With headquarters in Geneva, Switzerland, WIPO is one of the 16 specialized agencies of the United Nations system of organizations. It administers 23 international treaties dealing with different aspects of intellectual property protection. The Organization counts 182 nations as member states.

As of January 2000, all developed and developing countries who are members of the World Trade Organization (WTO) were obligated to have domestic laws and enforcement mechanisms that comply with the international standards set forth under the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). TRIPS, which is the most comprehensive multilateral agreement on intellectual property, includes a set of provisions dealing with domestic procedures and remedies for the enforcement of intellectual property rights. TRIPS lays down certain general principles applicable to all intellectual property rights enforcement procedures, and contains provisions on civil and administrative procedures and remedies, provisional measures, special requirements related to broader measures and criminal procedures. Because of the January 2000 deadline for TRIPS compliance, during much of that year, USPTO developed and implemented many training programs to help those countries with the January 2000 deadline to implement the TRIPS provisions. The USPTO will continue to cooperate with other US agencies and regional and international organizations in the years to come to provide similar programs to developing countries.

GENERAL PROVISIONS AND BASIC PRINCIPLES

Article 1

Nature and scope of obligations

1. Members shall give effect to the provisions of this Agreement. Members may, but shall not be obliged to, implement in their law more extensive protection than is required by this

Agreement, provided that such protection does not contravene the provisions of this Agreement. Members shall be free to determine the appropriate method of implementing the provisions of this Agreement within their own legal system and practice.

2. For the purposes of this Agreement, the term "intellectual property" refers to all categories of intellectual property that are the subject of Sections 1 through 7 of Part II.

3. Members shall accord the treatment provided for in this Agreement to the nationals of other members. In respect of the relevant intellectual property right, the nationals of other members shall be understood as those natural or legal persons that would meet the criteria for eligibility for protection provided for in the Paris Convention (1967), the Berne Convention (1971), the Rome Convention and the Treaty on Intellectual Property in Respect of Integrated Circuits, were all members of the WTO members of those conventions. Any member availing itself of the possibilities provided in paragraph 3 of Article 5 or paragraph 2 of Article 6 of the Rome Convention shall make a notification as foreseen in those provisions to the Council for Trade-Related Aspects of Intellectual Property Rights (the "Council for TRIPS").

Article 2

Intellectual property conventions

1. In respect of Parts II, III and IV of this Agreement, members shall comply with Articles 1 through 12, and Article 19, of the Paris Convention (1967).

2. Nothing in Parts I to IV of this Agreement shall derogate from existing obligations that members may have to each other under the Paris Convention, the Berne Convention, the Rome Convention and the treaty on Intellectual Property in Respect of Integrated Circuits.

Article 3

National treatment

1. Each member shall accord to the nationals of other members treatment no less favorable than that it accords to its own nationals with regard to the protection of intellectual property, subject to the exceptions already provided in, respectively, the Paris Convention (1967), the Berne Convention (1971), the Rome Convention or the Treaty on Intellectual Property in Respect of Integrated Circuits. In respect of performers, producers of phonograms and broadcasting organizations, this obligation only applies in respect of the rights provided under this Agreement. Any member availing itself of the possibilities provided in Article 6 of the Berne Convention (1971) or paragraph 1(b) of Article 16 of the Rome Convention shall make a notification as foreseen in those provisions to the Council for TRIPS.

2. Members may avail themselves of the exceptions permitted under paragraph 1 in relation of judicial and administrative procedures, including the designation of an address for service or the appointment of an agent within the jurisdiction of a member, only where such exceptions are necessary to secure compliance with laws and regulations which are not inconsistent with the provisions of this Agreement and where such practices are not applied in a manner which would constitute a disguised restriction on trade.

Article 4

Most-favoured-nation treatment

With regard to the protection of intellectual property, any advantage, favour, privilege or immunity granted by a member to the nationals of any other country shall be accorded immediately and unconditionally to the nationals of all other members. Exempted from this obligation is any advantage, favour, privilege or immunity accorded by a member:

(*a*) deriving from international agreements on judicial assistance or law enforcement of a general nature and not particularly confined to the protection of intellectual property;

(*b*) granted in accordance with the provisions of the Berne Convention (1971) or the Rome Convention authorizing that the treatment accorded be a function not of national treatment but of the treatment accorded in another country;

(*c*) in respect of the rights of performers, producers of phonograms and broadcasting organizations not provided under this Agreement;

(*d*) deriving from international agreements related to the protection of intellectual property which entered into force prior to the entry into force of then WTO Agreement, provided that such agreements are notified to the Council for TRIPS and do not constitute an arbitrary or unjustifiable discrimination against nationals of other Members.

Article 5

Multilateral agreements on acquisition or maintenance of protection

The obligations under Articles 3 and 4 do not apply to procedures provided in multilateral agreements concluded under the auspices of WIPO relating to the acquisition or maintenance of intellectual property rights.

Article 6

Exhaustion

For the purposes of dispute settlement under this Agreement, subject to the provisions of Articles 3 and 4 nothing in this Agreement shall be used to address the issue of the exhaustion of intellectual property rights.

Article 7

Objectives

The protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conductive to social and economic welfare, and to a balance of rights and obligations.

Article 8

Principles

1. Members may, in formulating or amending their laws and regulations, adopt measures necessary to protect public health and nutrition, and to promote the public interest in sectors of vital importance to their socio-economic and technological development, provided that such measures are consistent with the provisions of this Agreement.

2. Appropriate measures, provided that they are consistent with the provisions of this Agreement, may be needed to prevent the abuse of intellectual property rights by right holders or the resort to practices which unreasonably restrain trade or adversely affect the international transfer of technology.

Does the TRIPS Agreement Apply to all WTO Members?

All the WTO agreements (except for a couple of "plurilateral" agreements) apply to all WTO members. The members each accepted all the agreements as a single package with a single signature—making it, in the jargon, a "single undertaking".

The TRIPS Agreement is part of that package. Therefore it applies to all WTO members (more on the single undertaking).

But the agreement allows countries different periods of time to delay applying its provisions. These delays define the transition from before the agreement came into force (before 1 January, 1995) until it is applied in member countries. The main transition periods are :

- Developed countries were granted a transition period of one year following the entry into force of the WTO Agreement, *i.e.,* until 1 January, 1996.
- Developing countries were allowed a further period of four years (*i.e.,* to 1 January, 2000) to apply the provisions of the agreement other than Articles 3, 4 and 5 which deal with general principles such as non-discrimination.
- Transition economies, *i.e.,* members in the process of transformation from centrally-planned into market economies, could also benefit from the same delay (also until 1 January, 2000) if they met certain additional conditions.
- Least-developed countries are granted a longer transition period of a total of eleven years (until 1 January, 2006), with the possibility of an extension. For pharmaceutical patents, this has been extended to 1 January, 2016, under a decision taken by ministers at the Fourth Ministerial Conference in November 2001.

What is the Place of the TRIPS Agreement in the Multilateral Trading System?

One of the fundamental characteristics of the TRIPS Agreement is that it makes protection of intellectual property rights an integral part of the multilateral trading system, as embodied in the WTO.

The TRIPS Agreement is often described as one of the three "pillars" of the WTO, the other two being trade in goods (the traditional domain of the GATT) and trade in services.

The TRIPS Agreement is part of the "single undertaking" resulting from the Uruguay Round negotiations. That implies that the TRIPS Agreement applies to all WTO members. It also means that the provisions of the agreement are subject to the integrated WTO dispute settlement mechanism which is contained in the Dispute Settlement Understanding (the "Understanding on Rules and Procedures Governing the Settlement of Disputes").

What is the Relationship between the TRIPS Agreement and the Pre-existing International Conventions that it Refers to?

The TRIPS Agreement says WTO member countries must comply with the substantive obligations of the main conventions of WIPO—the **Paris Convention** on industrial property, and the **Berne Convention** on copyright (in their most recent versions).

With the exception of the provisions of the Berne Convention on moral rights, all the substantive provisions of these conventions are incorporated by reference. They therefore become obligations for WTO member countries under the TRIPS Agreement – they have to apply these main provisions, and apply them to the individuals and companies of all other WTO members.

The TRIPS Agreement also introduces additional obligations in areas which were not addressed in these conventions, or were thought not to be sufficiently addressed in them. The TRIPS Agreement is therefore sometimes described as a Berne and Paris-plus Agreement.

The text of the TRIPS Agreement also makes use of the provisions of some other international agreements on intellectual property rights:

- WTO members are required to protect integrated circuit layout-designs in accordance with the provisions of the **Treaty on Intellectual Property in Respect of Integrated Circuits (IPIC Treaty)** together with certain additional obligations.
- The TRIPS Agreement refers to a number of provisions of the **International Convention for the Protection of Performers, Producers of Phonograms and Broad-**

casting Organizations (Rome Convention), without entailing a general requirement to comply with the substantive provisions of that Convention.

TRIPS Agreement specifies that nothing in Parts I to IV of the agreement shall derogate from existing obligations that members may have to each other under the Paris Convention, the Berne Convention, the Rome Convention and the Treaty on Intellectual Property in respect of integrated circuits.

What is the Role of the TRIPS Council?

The TRIPS Council comprises all WTO members. It is responsible for monitoring the operation of the agreement, and, in particular, how members comply with their obligations under it.

1. Monitoring: Members review each others' laws.

The reviews are central to the TRIPS Council's task of monitoring what is happening under the agreement.

Each country has to make sure its laws comply with the obligations of the agreement, according to the timetable spelt out in the agreement. Most have to enact laws implementing the obligations.

These laws are notified to the TRIPS Council, allowing members to review each others' legislation, and promoting the transparency of members' policies on intellectual property protection. The requirement to notify comes under the TRIPS Agreement. Members have to supply the TRIPS Council with copies of their laws and regulations that deal with the TRIPS Agreements' provisions. These notifications are then used as the basis the Council's reviews of members' legislation. In these reviews, countries supply written questions about each others' laws before the review meetings. The answers are also in writing. Follow-up questions and replies are made orally during the course of the meeting, and further follow-up is possible at subsequent meetings.

PATENTING AND THE PROCEDURES INVOLVED IN THE APPLICATION FOR GRANTING OF A PATENT

Overview of the Patenting Process

A patent is an exclusive right of its owner to exclude others from making, using, or selling the invention as defined in the claims of the patent for a period of time, which in the United States is 20 years from the date of filing the patent application.

There are three types of patents:

1. Utility Patents may be granted to anyone who invents or discovers any new and useful process, machine, article of manufacture, or composition of matter, or any new and useful improvement thereof;

2. Design Patents may be granted to anyone who invents a new, original, and ornamental design for an article of manufacture; and

3. Plant Patents may be granted to anyone who invents or discovers and asexually reproduces any distinct and new variety of plant.

STEPS TO A PATENT

Introduction

There are several steps that help in securing a patent. The steps begin in the lab and move through the legal process of patent prosecution and maintenance. This section describes the

steps that you should follow to help maximize the value of your invention and protect your intellectual property rights.

(*a*) Patent success starts in the lab

Documentation is the beginning of strong patents because it authenticates with whom a theory originates (conception) and the steps taken to test and produce results (diligent reduction to practice). These documents are scrutinized to determine inventorship, reduction to practice, and to support a patent's validity.

Well-maintained laboratory records can document the date of conception of an invention and also establish diligence in developing an idea. Such documentation is needed in case of a question about which inventor should be entitled to pursue a patent. Records can be more useful in this regard if the following steps are followed:

- Records have more value if they are meaningful to others. Entries should be complete, accurate, and legible.
- Preface the record of each experiment with a brief purpose or statement of the problem.
- Use a permanently bound notebook with numbered pages.
- Make frequent entries (daily is best) in ink, and design and date each page.
- Start a new page for each new experiment.
- Draw a continuous diagonal line through unused portions of pages remaining at the end of an experiment.
- Don't erase. Instead, where necessary, cross out with a single line.
- Initial and date all major changes.
- Record observations of physical results even if they are not fully appreciated or understood at the time.
- Have work corroborated by having notebooks witnessed by dated signature of an associate who understands the content, but not a co-worker or one who collaborates in the research area and who could be a joint inventor.
- Think carefully before destroying any samples, run sheets, or records related to any inventions.

(*b*) Plan to both publish and patent

Although the timing of publications may sometimes prohibit patenting, planning allows the inventor to both publish and patent. Disclosing the idea to the Office of Technology Transfer as soon as the invention is clearly conceptualized, or at least before submitting abstracts or manuscripts disclosing the invention, allows time to complete a patentability and commercialization assessment before being barred from a patent.

In the United States, an inventor has a grace period of one year to file a patent application after disclosure through publication. However, if an invention is publicly disclosed before a U.S. patent application is filed, patent rights in most other countries are lost.

What constitutes publication? Articles in newspapers, newsletters, bulletins, textbooks, journals, theses, reports, and even letters to the editor all qualify as publications. Oral presentations may constitute publication, as would distribution of a paper at a public meeting. Some legal experts also think that disclosure through electronic communications, such as e-mail, may be considered publication. The key test is that the publication be enabling—it must describe the invention in sufficient detail that it could be duplicated or put into use.

(*c*) Disclosing an invention

The technology transfer process actually begins when the inventor discloses his or her potential invention to the Office of Technology Transfer—a step required by IU's intellectual-property-policy.

Discussions between the inventor and office staff members can help determine whether an invention has been made and whether a formal disclosure should be completed. The office staff supplies inventors with a formal disclosure form and assists in its preparation.

An invention disclosure is a written record of an invention containing a complete description of the invention, the inventor's dated signature, and dated signatures of witnesses who fully understand the invention (but are not joint inventors).

(*d*) Invention evaluation

When the completed disclosure form has been reviewed by the Office of Technology Transfer and discussed with the inventor, recommendations are formulated on ownership, patenting, and licensing. Inventions are evaluated for novelty, likelihood of patentability, potential market, usefulness, projected development time, and cost. The most effective way to bring the invention's benefits to the public will be determined, whether through patent, copyright, or placing the invention in the public domain (usually through publication).

The probability for an invention's economic success may be roughly gauged by these questions:

- How big is the potential market for the invention? Can the invention be sold to a large section of the public or a large number of manufacturers? Can it be sold to different industries?
- What development will be required before the invention can be sold? How long will development take? What will it cost? What regulatory requirements must be satisfied?
- How will the product be marketed? Can it be distributed through normal commercial channels?
- What is the demand for the invention? Does it fill a real need and not just replace satisfactory article? Does it contribute to the interest?

In most cases, before a patent application is prepared, the Office of Technology Transfer staff will search for potential licensees to determine the level of industrial interest in the technology. (A license is essentially an agreement by the patent owner not to sue the licensee for infringement as long as the licensee abides by the agreement. Licensing is typically the way the university realizes an invention's commercial potential). In most cases, commercial organizations will underwrite patent expenses in return for the right to a license.

(*e*) Patent prosecution (process of obtaining a patent)

The process of obtaining a patent is called patent prosecution. It consists of preparing and filing the patent application, then filing responses and amendments to the objections of the patent examiner. Patent prosecution will result in either the issuance of a published patent or the rejection or abandonment of the application.

Under U.S. law, individual inventors are allowed to prosecute their own patent applications. However, because the Patent and Trademark Office has specific and often complex rules about the content and examination of applications and because patents are interpreted and enforced in court, inventors should be represented by a patent attorney or agent.

To qualify as a patent attorney, an individual must have a law degree and a degree in a technical area, and the person must pass the rigorous patent bar exam. To become a patent agent, a person still must pass the patent bar exam, but a law degree is not required.

The patent application is prepared by the patent attorney with the help of the inventor and is similar in many respects to a detailed scientific paper (the specifications and drawings) accompanied by one or more claims, which make-up the legal definition of the invention. The patent application must make a full disclosure of the invention to teach others how to make and use the invention and to clearly define the borders of the patent protection. Accomplishing both these objectives requires the close collaboration of the inventor and the patent attorney.

Although the make-up of patent applications varies considerably, it is commonly divided into the following headings:

- **Field of the invention —** This describes the general technological field and the broad nature of the invention.
- **Background of the invention —** The background describes the technological problem to be solved and gives a brief description of present technology and its limitations.
- **Objectives of the invention —** The objectives indicate the nature of the improvements the invention seeks to provide.
- **Summary of the invention —** The summary states the essential elements of the invention in broad terms and often introduces the terminology to be used in the main claims of the patent.
- **Detailed description of the invention and/or description of the drawings —** These details include the experimental data, given by way of example, describing the methodology of the invention and the apparatus used (if any).
- **Claims —** Claims define the invention in one or more single-sentence paragraphs and serve as the legal definition of the invention.

When received in the Patent and Trademark Office, the application package is assigned to a patent examiner with expertise in the invention's technical field. Although work loads and response times vary, usually six months or more pass before the application's initial examination. In the initial examination, the examiner searches both the scientific and the patent literature to determine whether the application discloses and claims new and patentable subject matter, and the examiner judges the allowability of each claim. Most applications are initially rejected. The basis for rejection is most often prior patents or publications which, in the examiner's view, render the new invention obvious. The patent attorney, with the assistance of the inventor, responds to the examiner with arguments about why the invention is patentable. The cycle can be repeated several times and the patent application can be amended, restricted, divided, or continued in the process.

On average, the examination of a patent application takes two years in the United States, where the application is considered confidential throughout the process. In many other countries, patent applications are published after a given period of time.

The Patent and Trademark Office allows, or approves, around 90,000 patents a year. The total number of patents issued now exceeds 5 million. When the Patent and Trademark Office gives notice of allowance, and the issue fee is paid, the patent is issued, or published in the Patent Gazette.

The cost of the typical U.S. patent prosecution for university, conducted by outside legal counsel, is $15,000 or more.

Summary of Legal Process from the Inventor's Perspective

Filing a Patent Application

Office of Technology Transfer (OTT) submits the invention disclosure to a patent attorney

↓

Patent attorney determines patentability and with the aid of the inventor(s), drafts a application for review

↓

Application is filed along with an assignment, declaration, and power of attorney

↓

Provisional

After 1 year the application must be Converted to a PCT application

Regular

After 1 year the foreign placeholder called a PCT application is filed

↓

18 months after the first US filing, the PCT will publish

↓

18 months after the PCT is filed, the PCT must be converted to a separate application per each foreign country ("nationalization"). Because nationalization is extremely expensive, the university does not nationalize without corporate sponsorship.

Examination of a Patent Application

Patent offices worldwide correspond with applicants through official "office actions". The patent attorney and ARTI work with the inventor(s) to answer each office action the time allotted (typically 3 months from the date the examiner issues the action).

↓

A successful prosecution results in a "notice of allowance" from the patent office indicating that the examiner has accepted claims that will "issue" in a patent.

Maintenance of a Patent

Maintenance fees must be paid 3.5, 7.5, and 11.5 years after the patent is issued.

↓

All patent applications filed after June 8, 1995 expire 20 years from the filing, while applications filed before this date expire 17 years from the date the patent was issued.

COMPULSORY LICENSES

Compulsory licensing system has become a typical feature of patent laws; it has also been widely adopted in other areas of intellectual property rights. Developed countries have largely

relied on such licenses in order to limit exclusive rights and prevent or remedy abusive practices in several areas. The study reveals there is a broad range of grounds under which compulsory licenses may be granted in both developed and developing countries. The grounds and conditions on which compulsory licenses have been regulated and granted in developed countries illustrate the flexibility and potential of the compulsory licensing system to address a multiplicity of public interests and concerns. The evidence also indicates that arguments—often voiced by the developed countries' business community and governments—against compulsory licenses as a deviation from acceptable standards for intellectual property rights, are not reflected in the policies actually applied in such countries.

Three Main Conclusions Particularly Relevant for Developing Countries may be Drawn from the Previous Analysis.

- Compulsory licenses should be considered as an essential element in patent laws and other intellectual property regimes. Developing countries should disregard any attempts by developed countries to limit under bilateral or other agreements the scope of and grounds for compulsory licensing.
- The grounds and conditions for compulsory licenses should be carefully determined by national laws. The extent to which such licenses would be available and effective depend on the provisions of national legislation and on its adequate administration by informed national authorities.
- Developing countries should preserve the maximum possible freedom under international rules to design their compulsory licensing systems, according to their own interests and needs, including in such areas as the protection of health and the environment, and the promotion of transfer of technology and local industrialization. Should the issue of compulsory licenses be included in the agenda of possible future negotiations in WTO, developing countries should seek to clarify the scope for the granting of such licenses in certain cases (*e.g.,* of non-exploitation), as well as to remove some of the restrictive conditions imposed by the said TRIPs Agreement.

Grounds for Granting Compulsory Licenses

As mentioned above, compulsory licenses may be granted on diverse grounds, to be determined by national laws. The different modalities of compulsory licenses are briefly reviewed in this section. The use of such licenses in other fields of intellectual property fields is also mentioned in order to illustrate the broad use of this mechanism.

1. Refusal to deal

In principle, the right of the patent owner to give or not give a license to a third party is recognized. In some jurisdictions this is considered an essential element of intellectual property rights, as stated in Berkey Photo Inc. vs. Eastman Kodak Co. (1979) in the United States, and in the case of Volvo AB vs. Erik Veng (UK) Ltd. (1989) in Europe (Breier, 1999, p.274).

The UK law authorizes the granting of compulsory licenses when, by reason of the conditions imposed by the patentee on the grant of a license, a market for the export of any patented product made in the United Kingdom is not being supplied, the working or efficient working of any other patented invention which makes a substantial contribution to the art is prevented, or the establishment or development of commercial or industrial activities is unfairly prejudiced (Article 48(3)(d)).

Questions have also been raised recently in the United States regarding whether "the refusal to deal" (that is, the refusal to grant a license on reasonable terms) may be anti-competi-

tive when this allows a patentee to block follow-on research, particularly if the initial patent is overly broad (McFetridge, 1998, p.91).

An example of how a compulsory license can be based on "refusal to deal" is provided by a decision of the European Court of Justice of 6 April 1995 in the Magill case. In its judgement, the court confirmed that Radio Telefis Eireann (RTE) and Independent Television Publications Limited (ITP), who were the only sources of basic information on programme scheduling, which is indispensable raw material for compiling a weekly television guide, could not rely on national copyright provisions to refuse to provide that information to third parties. Such a refusal, the court held, in this case constituted the exercise of an intellectual property right beyond its specific subject matter and, thus, an abuse of a dominant position under Article 86 of the Treaty of Rome.

The court argued that RTE and ITP held a dominant position, because they were the only source in Ireland of the basic information necessary to produce weekly television programming guides and were thus in a position to reserve for themselves the secondary market for weekly television guides by excluding all competition from that market. The court considered that, whilst refusal to grant a license in exercising an intellectual property right is not of itself an abuse of a dominant position, it may be an abuse where special circumstances exist. Such circumstances included the lack of an actual or potential substitute for a weekly television guide, the existence of a specific, constant and regular demand for such a guide, and the fact that the refusal to grant a license to Magill to produce such a guide prevented the appearance of a new product on the market which RTE and ITP did not offer (Latham and Geissmar, 1995, p.9).

A decision by the Belgium court in 1995 also imposed a compulsory license on two copyright collecting societies in favor of two cable distributors who had been refused the right to transmit by cable in Belgium programmes from the German Cable SATI. Refusing the authorization for a reasonable remuneration was deemed to be abusive (Latham, 1996, p.25). In Australia, compulsory license for "refusal to deal" may be granted unless the patentee can prove that it would equally refuse to license in a competitive situation (O'Bryan, 1992, p.10).

(The "refusal to deal" as a ground for granting a compulsory license has been provided in many national laws, such as the patent laws of China, Argentina and Israel).

In the United Kingdom and in other countries that have followed the model of UK legislation, "refusal to deal" may lead to a compulsory license when an export market is not being supplied, the working of any other patented invention which makes a substantial contribution is prevented or hindered, or the establishment or development of commercial or industrial activities in the country is unfairly prejudiced (Section 48.3.d of the UK Patent Act, as revised in 1977). Similarly, in South Africa, a license can be granted in the case of the refusal to grant a license on reasonable terms, where trade or industry or agriculture or the establishment of a new trade or industry in the country is prejudiced, and it is in the public interest that a license be granted (Section 56(2)(d), Patents Act No. 57 of 1978).

The hypothesis of "refusal to deal" has also been provided for in the area of breeders' rights. For instance, the law of Poland on plant varieties protection (1987) stipulates that a compulsory license may be granted when the title-holder does not offer a license allowing third parties to meet unsatisfied needs of the national economy, or makes the grant of a voluntary license subject to unfair conditions (Article 29).

2. Non-working and inadequate supply

As mentioned, the origin of compulsory licenses is linked to the obligation to work a patent. Following the Paris Convention, a large number of developed and developing countries estab-

lished compulsory licenses for lack of or insufficient working. In the laws of Austria, France and Japan (Fauver, 1988, p. 672), this obligation was generally understood as the *industrial* use of the invention. But in many developed countries this concept was gradually replaced by the *commercial* use of the invention. In other world, the obligation to work a patent could be satisfied by means of the mere importation of the protected product.

For instance, the introduction into, or the sale in the territory of, Italy of items manufactured in foreign countries was not considered by Italian law to constitute working of the invention. However, in 1992 the European Court of Justice condemned Italy and established that the working requirement was satisfied on the domestic market by imports of products manufactured in another EC member state. The court held that if, after 3 years from the date of grant of a patent, or 4 years from the filing date of the application, the proprietor of a patent or his successor in title has not worked the patented invention, directly or through one or more licensees, by way of production in the territory of the state, or by way of importation from one of the member states of the European Community, or has worked it to an extent seriously disproportionate with the needs of the country, a compulsory license for the non-exclusive use of the invention may be granted to any person applying for it.

A similar development took place in Spain, which has changed its law to address the compulsory licensing provisions of the TRIPs Agreement. The Spanish patent law now provides that:

"The exploitation of the patented invention by means of imports coming from the practising of the invention in a member state of the World Trade Organization shall have the same effect as the practising of the invention in the national territory".

In some countries (for example, the United Kingdom), the granting of a compulsory license has been linked to the insufficiency of supply on reasonable terms, including the supply of export markets.

Compulsory licenses for inadequacy of supply have been provided for in some laws relating to the protection of design laws such as in the United Kingdom and Ireland, despite the fact that the Paris Convention established that they shall not be subject "to any forfeiture, either by reason of failure to work or by reason of the importation of articles corresponding to those which are protected" (Article 5B).

Such licenses are also found in many national laws on breeders' rights. For instance, the laws of Argentina (1973), New Zealand (1987, as amended in 1994) and Poland (1987) provided for such licenses when the supply of the cultivar is not adequate in terms of quantity, quality and/or price. Similarly, in the United States a variety may be declared of "open use" when the owner is unwilling or unable to supply the public needs for the variety at a fair price.

Finally, in the area of copyright, under the Berne Convention a compulsory non-exclusive and non-transferable license is available in developing countries to publish in printed form certain works if, after three years following the publication of a work, a translation of that work has not been published in a language in general use in the developing country, or if the relevant translations are out of print. The period of three years can be reduced by agreement, but not to less than one year. Furthermore, such reduction of time is not permissible where the relevant language is English, French or Spanish.

Furthermore, no license obtainable under the provisions referred to can be granted before a period of six months after the three years has elapsed so as to give the author the opportunity to publish a translation in the appropriate language. The license is also limited so as to apply only for the purposes of teaching, scholarship or research. The license can be terminated if the owner of the right produces a translation at a reasonable price subsequent to the license being

granted. In recognition of authors' moral rights, no license can be granted if the author has himself/herself withdrawn from circulation all copies of the work.

Likewise, developing countries can grant non-exclusive non-transferable licenses to publish works where copies of an edition have not been distributed in the country to the general public by the owner of the right at a price reasonably related to that normally charged in the country for comparable works. This right is subject to similar limitations as those referred to in the preceding paragraphs.

3. Public interest

The "public interest" is established in many laws as a ground for compulsory licenses. The concept of what constitutes the "public interest" varies amongst countries and over time. It will be the task of the courts or administrative authorities to judge when the public interest is to be ensured or protected via the granting of a compulsory license. Thus, in certain jurisdictions such as the United States, it has been argued that insufficient working, the dependency of patents, or the interest of consumers in obtaining a protected product at the lowest possible price, do not constitute a sufficient basis for the granting of compulsory licenses on grounds of public interest (Beier, 1999, p. 265). However, in countries with limited industrial development, "public interest" may be deemed to include the opportunity to develop national industry.

However, the US government has created compulsory licenses when it felt that the country's public interest was at stake. Such is the case of the Atomic Energy Act (42 U.S.C.A. Sec. 2183) and of the Clean Air Act (1970) which sets forth particular situations where a private party could demand a license from a US patent owner. The "energy crisis" of 1973 also provides a good example. As part of the government's policy to overcome national dependency on one source of energy and the inflationary effect of the increases in oil prices, the Federal Non-Nuclear Energy Research and Development Act (ERDA) was passed in 1974 (42 U.S.C.A. Sec. 5908 (n)), under which the Administration of ERDA was mandated to make recommendations on compulsory licensing.

The German patent law authorizes compulsory licenses to be granted when "it is indispensable for the public interest". A compulsory license has been granted in only one instance by the German Federal Patent Court, on June 7, 1991. The applicant (Bioferon) manufactured a pharmaceutical product (polyferon) for the treatment of chronic polyarthritis and obtained approval, under the pharmaceuticals law, for application of the product. The applicant also held dependent patents in respect of specified uses of human immune interferon. The Federal Patents Court found that there was a public interest in the medical use of polyferon which was dependent upon the dominant substance patent on human immune interferon.

The Federal Supreme Court disagreed with the Federal Patent Court and in December 1995 it decided that "a compulsory license cannot be granted for a pharmaceutical if the public interest can be satisfied with other, more or less equivalent, alternative preparations".

The Supreme Court based its decision on the fact that the substantially improved therapeutic properties of the license's applicant (Bioferon) as compared to conventional medications had not been established. However, according to two commentators,

"The fact that the Federal Supreme Court — in contrast to the Federal Patent Court — refused the grant of a compulsory license in the present case cannot be understood as an entire rejection of the instrument of the compulsory license. It should be emphasized that, in the opinion of the Federal Supreme Court, the petitioner was not successful in proving from a medical viewpoint that, instead of an advantageous use of "polyferon", no other similarly effective preparation for the treatment of rheumatoid arthritis is available".

The granting of compulsory licenses on grounds of public interest have been provided for in the patent laws of some developing countries, such as Argentina and the Andean Group (Decision 344). They have also been established in breeders' rights legislation, including in the most recent laws on the matter. The granting of compulsory licenses is recognized in the UPOV Convention, as revised in 1991, only for reasons of "public interest" (Article 17) and against an "equitable remuneration".

4. Anti-competitive practices

Although in the United States the patent law does not provide for compulsory licenses, this is probably the country with the richest experience in the granting of compulsory licenses to remedy anti-competitive practices. More than one hundred such licenses have been granted. Compulsory licenses have been granted in the United States in relation to present and future patents. Generally such licenses have been granted against a reasonable royalty, generally determined on the basis of the "willing-buyer, willing-seller" formulation. However, in some cases, the compulsory licenses were conferred royalty free. In some cases, moreover, the patentee was required to make the results of its research readily available to other industry members, or to transfer the know-how actually used in production.

EARLIER EXAMPLES OF COMPULSORY LICENSES GRANTED BY COURTS IN THE UNITED STATES UNDER THE ANTITRUST LEGISLATION

1. *Hartford-Empire Company vs. U.S., 65 United States Patent Quarterly (USPQ) 1 (1945).*

The Supreme Court held that the defendants violated the antitrust law (Sherman Act and Clayton Act), and it required them to grant licenses under their glassmaking machinery patents at "uniform reasonable royalties". The court stated that it had no authority to order dedication of the patents which would be equivalent to royalty-free compulsory licensing.

2. *U.S. vs. National Lead Company, 73 United States Patent Quarterly (USPQ) 498 (1947).*

The Supreme Court used compulsory licensing with royalty payments to promote competition where the defendants conspired or combined to restrain trade in titanium products. The court stated that royalty-free compulsory licensing was an open matter to be decided in a future case. The decision did provide for the licensing of technology at a reasonable charge and limited to a three year period.

3. *U.S. vs. General Electric Company, 99 United States Patent Quarterly (USPQ) 76 (1953).*

The District Court ordered the granting of licenses at reasonable royalties under patents acquired within five years of the decree.

4. *U.S. vs. Glaxo Group Limited, 176 United States Patent Quarterly (USPQ) 289.*

The US Supreme Court held that the government may litigate the validity of a patent, despite the fact that the defendant did not rely on the patent as defense against antitrust claims, where patent licenses and pooling agreements are *per se* unreasonable restraints on trade, and where the government's claims for further relief are substantial. The court stated that mandatory sales and reasonable royalty licensing are well established forms of relief when necessary to an effective remedy, particularly where patents have provided leverage for, or have contributed to, and antitrust violation.

5. *U.S. vs. Copper Development Association, Inc.*

The government charged 11 copper fabricating companies and their trade association with

violating Section 1 of the Sherman Act by conspiring to unlawfully restrict rights granted under jointly-owned patents for a single stack plumbing system. The government proposed a consent decree wherein the defendants agreed to license their patents and furnish technical data upon request at royalties not to exceed three per cent of the net selling price of certain components of the system.

6. *U.S. Manufacturers Aircraft Association, Inc.*

The government charged the defendants with violating Section 1 of the Sherman Act by utilizing patent pooling and cross-licensing arrangements to eliminate competition in research and development of aircraft inventions. The consent decree dissolves the association, cancels the cross-licensing arrangement, and provides for compulsory licensing of about 1,500 US patents at reasonable royalties.

RECENT EXAMPLES OF COMPULSORY LICENSES IN THE UNITED STATES UNDER ANTITRUST LEGISLATION

1. *Ciba-Geigy* and *Sandoz merger*

The US Federal Trade Commission (FTC) issued on 24 March 1997, a Decision and Order concerning the merger between Swiss companies Ciba-Geigy and Sandoz into Novartis. The combined entity would also control Chiron, a biotechnology company. The FTC concluded that the merger would violate US antitrust laws, because the merged companies are current or potential competitors for several products. The FTC required divestiture of several products, and ordered compulsory licenses of intellectual property rights for a number of other healthcare inventions. For example, Ciba-Geigy, Sandoz and Chiron were required to license a large portfolio of patents, data and know-how relating to HSV-tk products, hemophilia gene rights and other products to Rhone-Poulenc Rorer. The new merged entity and Chiron were also required to grant non-exclusive licenses to any interested party of patents and other rights relating to Cytokine products. In the case of the non-exclusive Cytokine licenses (which involve gene therapy), and the Anderson gene therapy patent, the FTC specified that the royalties can be no greater than three per cent of the net sales price.

2. *Gargoyles, Inc.* and *Pro-Tec, Inc. vs The United States*

On 20 May 1997, a decision was given by the United States Court of Appeals for the Federal Circuit (96-5089-5094; 113 F.3 d 1572). In this case, the private plaintiff -- who owned a patent subject to compulsory licenses -- sought "lost profits" rather than a "reasonable royalty" as compensation. The royalty set by the Court of Federal Claims was 10 percent. The government considered this excessive and sought a reduction. The dispute involved US patent 4,471,611 for protective eyewear, which had been used by American Optical to provide the US Army with several thousand pairs of ballistic/laser protective spectacles. The Appeals Court upheld the lower court decision and argued that "because recovery is based on eminent domain, the proper measure is what the owner has lost, not what the taker has gained."

3. *Acquisition of shares of Rugby-Darby Group Companies by Dow Chemical Co.*

The FTC required Dow to license to a potential entrant intangible dicyclomine assets, including "all formulations, patents, trade secrets, technology, know-how, specifications, designs, drawings, processes, quality control data, research materials, technical information, management information systems, software, the drug master file, all information relating to the United States Food and Drug Administration Approvals" that are not part of the acquired company's physical facilities or other tangible assets.

4. *Upjohn and Pharmacia Aktiebolag merger*

Upjohn was required to divest certain intellectual property (including patents), or the FTC would appoint a trustee to issue an exclusive United States license and a non-exclusive rest-of-the-world license for Pharmacia's research and development assets related to 9-AC. These requirements would protect consumers from reduced competition and higher prices for topisomerase 1 inhibitors.

5. *Governmental use*

Under the 1883 UK patent act, the Crown was entitled to use patented inventions without the assent or the compensation of the patentee, though it was practice to reward the patentee *ex gratia*. According to the 1977 Act, compulsory licenses (relating to granted patents or applications) for government use are available for the "Crown services", against a remuneration except when the invention has been recorded by, or tried by, or on behalf of a government department before the relevant priority date otherwise than in consequence of a communication made in confidence directly or indirectly from the patentee. The license may be used by any person so authorized by a government department. The Crown enjoys the qualified right to sell other than for purposes of foreign defense or for production or supply of specified drugs and medicines (Young et al., 1994, pp. 477).

The US government has also made extensive use of compulsory licenses for governmental use. The governmental use of a patent is regarded as based on "eminent domain". The government's powers may be delegated to a contractor, who would act on its behalf. The government cannot commit the tort of a patent infringement, but can only be held liable to pay reasonable compensation.

The extensive use of governmental licenses in the United States has raised complaints from the European Union. According to the EU,

"Under US law (28 US Code Section 1498) a patent owner may not enjoin or recover damages on the basis of his patent for infringements due to the manufacture or use of goods by or for the US Government of Defense but is also extremely widespread in practically all government departments. For obvious reasons this practice is particularly detrimental for foreign rightholders because they will generally not be able to detect governmental use and are thus very likely to miss the opportunity to initiate an administrative claims process.

Article 31 of the TRIPS Agreement introduces a requirement to inform promptly a right holder about government use of his patent, but no action has been taken by the US so far to bring their legislation into conformity with this provision" (European commission, 1997).

6. *Facilitate the use of dependent patents*

The TRIPS Agreement, as well as numerous national laws, permits the granting of compulsory licenses, when the use of an invention (a dependent invention) is not possible without infringing another (the principal invention). The Agreement sets out a number of conditions which have to be met if such licenses are to be granted. However, there is considerable scope for flexibility in the interpretation of those provisions, in particular with respect to evaluating the economic and technical importance of the dependent invention.

In the case of these compulsory licenses, the owner of the principal patent can benefit not only from compensation paid for the use of his/her patent, but also from the right to use the dependent patent.[30]

A recent example of a compulsory cross-licensing license is provided by the European Directive on Biotechnological Inventions, which allows a breeder to request a compulsory license when he/she cannot acquire or exploit a plant variety without infringing a prior patent (Article 12.1). This would apply, for instance, when a breeder wishes to use a commercially available

variety for further breeding. Though he/she could do that under plant variety protection laws (protected by the "breeders' exemption"), the owner of a patent on certain genes expressed in the variety may claim infringement of his/her patent.

The Directive referred to above also provides for compulsory licenses for the reverse situation, in which it is the patent holder who can not use a protected variety without infringing third parties' rights (Article 12.2). This right may disadvantage plant breeders, since it may be sufficient for a company to insert a gene in an existing variety to claim the right to obtain a compulsory license. A number of conditions, however, set out in article 12.3 need to be complied with in order to obtain that license.

7. *Compulsory licenses for medicines*

In some countries, compulsory licenses have been provided for some specific products, such as pharmaceuticals and food. The TRIPS agreement has, in principle, prohibited this type of license, as national laws can not discriminate in the exercise of patent rights on the basis of the field of technology (Article 27.1). However, such licenses have proven to be an important tool to promote competition and to lower prices of protected products, as indicated below.

In Canada, compulsory licensing in respect of medicines was first introduced in 1923. The Patent Act, SC 1923 c 23, allowed for compulsory licenses to be granted for the manufacture, use and sale of patented medicines.

In 1969, the Canadian Patent Act was amended. The grant of compulsory licenses became admissible for importation (not only manufacturing) of a patented medicine. After the 1969 revision, a large number of compulsory licenses were granted against a 4 percent royalty on net sales prices, the royalty was divided by the number of patents at stake if the medicine was composed of different active ingredients.

As a result of the compulsory licensing system, a significant reduction in prices for medicines was reported in Canada. In 1983, compulsory licensing reduced the cost to consumers of the drugs so licensed by US$ 211 million, and the compulsory licensing system was found by the Commission of Inquiry on the Pharmaceutical Industry (also known as the "Eastman Commission") as an "effective component of an appropriate patent policy for the pharmaceutical industry" (p. xix). In 1991–1992 (just before the repeal of the system), compulsory licensed generics were priced at 55.6 percent of the equivalent brand name product; in the first year of marketing the generics price was 70 percent of the brand name price. The savings for the consumer in 1991–1992, were estimated at US$ 171 million.

As of 7 December 1987, amendments to the Patent Act were introduced that restricted the use of compulsory licenses for patented medicines. While compulsory licensing in respect of pharmaceuticals was retained, the Patent Act deferred the exercise of compulsory licenses with respect to the importation of a patented medicine for 10 years after the date of the first notice of compliance was published in respect of the patented medicine, while compulsory licenses for the manufacture of the product would only be available after seven years from that date. This restriction on the manufacture of medicine only related to sales for consumption in Canada. Consequently there was no deferral in respect of medicines manufactured in Canada for the export market.

In addition, where the medicine had been invented and developed in Canada, Section 39.16 of the Patent Act, provided that a compulsory license was only available for the making and not the importation of the medicines; and the making of the medicine under such a license was deferred for at least seven years and could be deferred for the life of the patent unless the Commissioner of Patents found upon application that the patentee or a voluntary licensee was not making the medicine in Canada for the purposes of completely or substantially supplying the Canadian market for the medicine. This regime was supplemented by a monitoring of the prices of new patented medicines by the "Patent Medicines Prices Review Board".

Shortly after this amendment, Canada abrogated the compulsory license system in order to comply with the country's commitments under the TRIPS Agreement. Bill C-91 was approved for that purpose in February 1993, but it applied retroactively as of 20 December 1991, the date on which the TRIPS Agreement was deemed to become known. The compulsory license system was replaced by the supervision and control of the prices of patented medicines. The powers of the Patent Medicines Prices Review board were enlarged so as to cover the prices of both new and existing medicines. The Board, among other measures, can order the patent owner to reduce the price of its medicine.

Compulsory licenses specifically related to medicines have been provided in other countries as well. For instance, French law authorizes them when medicines are "only available to the public in insufficient quantity or quality or at abnormally high prices". In Israel, a license can be granted if it is necessary to assure the public of a reasonable quantity of a product capable of being used as a medicament, or to manufacture a medicament or a patented process for manufacturing the latter.

PATENT COOPERATION TREATY (PCT)

Done at Washington on June 19, 1970, amended on October 2, 1979, and modified on February 3, 1984, and Regulations under the PCT (as in force on January 1, 1985) World Intellectual Property Organization, Geneva 1985.

The Contracting States

↓

Desiring to make a contribution to the progress of science and technology

↓

Desiring to perfect the legal protection of inventions

↓

Desiring to simplify and render more economical the obtaining of protection for inventions where protection is sought in several countries

↓

Desiring to facilitate and accelerate access by the public to the technical information contained in documents describing new inventions

↓

Desiring to foster and accelerate the economic development of developing country through the adoption of measures designed to increase the efficiency of their legal systems, whether national or regional, instituted for the protection of inventions by providing easily accessible information on the availability of technological solution applicable to their special needs and by facilitating access to the ever expanding volume of modern technology

↓

Convinced that cooperation among nations will greatly facilitate the attainment of these aims

↓

Have concluded the present Treaty

Establishment of a Union

1. The States party to this Treaty (hereinafter called "the Contracting States") constitute a Union for cooperation in the filing, searching, and examination, of applications for the protection of inventions, and for rendering special technical services. The Union shall be known as the International Patent Cooperation Union.

2. No provision of this Treaty shall be interpreted as diminishing the rights under the Paris Convention for the Protection of Industrial Property of any national or resident of any country party to that Convention.

Definitions

For the purposes of this Treaty and the regulations and unless expressly stated otherwise :

(*i*) "application" means an application for the protection of an invention; references to an "application" shall be construed as references to applications for patents for inventions, inventors' certificates, utility certificates, utility models, patents or certificates of addition, inventors' certificates of addition, and utility certificates of addition;

(*ii*) references to a "patent" shall be construed as references to patents for inventions, inventors' certificates, utility certificates, utility models, patents or certificates of addition, inventors' certificates of addition, and utility certificates of addition;

(*iii*) "national patent" means a patent granted by a national authority;

(*iv*) "regional patent" means a patent granted by a national or an intergovernmental authority having the power to grant patents effective in more than one State;

(*v*) "regional application" means an application for a regional patent;

(*vi*) references to a "national application" shall be construed as references to applications for national patents and regional patents, other than applications filed under this Treaty;

(*vii*) "international application" means an application filed under this Treaty;

(*viii*) references to an "application" shall be construed as references to international applications and national applications;

(*ix*) references to a "patent" shall be construed as references to national patents and regional patents.

EXAMPLES OF PATENTS IN BIOTECHNOLOGY

In recent years, society has witnessed the explosive growth of biotechnology research. Much of this research has had a profound effect on our perception of the fundamental fabric of life itself. However, because of the complex nature of these discoveries, commercialization is often a long and expensive process. As a result of the need to achieve a proprietary position over this technology and the investment entailed in its commercialization, the field has seen phenomenal growth in the number of biotechnology patent applications which have been filed.

Intellectual property is a term used to describe property that is not tangible, but which instead originates through the creative effort of the inventor. Such property can be further characterized as a trademark, a copyright, a trade secret, or a patent. These divergent areas have in common a highly abstract concept of property.

(*a*) **Trademarks** include words, names, slogans, logos, and symbols which are used to *indicate the source* of a product or service. A trademark owner has the right to stop the commercialization of competitive goods having trademarks which are *confusingly similar* to those of the trademark owner.

(*b*) A **copyright** is the right to the exclusive publication, reproduction, adaptation, display, and performance of an original work which is fixed in a tangible medium of expression. A copyright protects the expression of an idea, but not the idea itself.

(*c*) A **trade secret** can be patentable and, unlike patents, is potentially indefinite in duration. However, the value of a trade secret is lost once it is disclosed. Also, the holder of a trade secret has no cause of action against those who independently discover the trade secret. From a societal standpoint, probably the greatest disadvantage of a trade secret is that, by its very nature, the trade secret may die with the owner. For example, the methods of treating wood employed by the famous violin maker, Stradivarius, have been lost forever. It was partly in response to the drawbacks of trade secret protection, as embodied by the Guild System of Medieval Europe, that the **patent system** was established.

The public policy behind the patent system is to encourage inventors to share their discoveries with the general public and thereby advance the general status of technology. The advancement is accomplished by encouraging innovation through giving the inventor the right of exclusive commercial use, and by encouraging competitors to design around the invention. Thus, the knowledge of the inventor is preserved for the benefit of society and future generations.

In the U.S., patent can be further categorized as design, plant, and utility patents. A **design patent** can be obtained for a new, original, and ornamental design; the invention covered by the design patent must not be for a characteristic which is primarily functional. For example, a design patent application might be filed for a pitcher which has a particularly attractive handle. If it were found that the handle of the pitcher were primarily functional (for example, it provided a better grip), then a design patent would not be appropriate.

Under the **Plant Patent** Act (PPA), patent protection is available for new varieties of asexually-reproduced plants. Protection under the PPA is very narrow; only one claim is permitted, and it covers only the whole plant. Thus, under the PPA, it is not possible to claim seeds, fruit, cells, or any other part of a plant which may be of commercial value. Also, because the PPA covers only plants which are asexually reproduced, such as roses and other ornamental plants, many agriculturally important plants cannot be protected under the PPA.

The most important type of patent, from a scientific and commercial standpoint, is the **utility patent.** From the standpoint of the inventor, the purpose in trying to obtain a utility patent is to secure the exclusive right to make, use and sell the patented invention. Those exclusive rights exist for the term of the patent. Patent terms were recently changed: (1) for applications filed after June 8, 1995, the term of any patent that issues will be 20 years from the first effective United States filing date of the application; (2) for applications on file on or before June 8, 1995, and for patents in force on June 8, 1995, the term of the patent is the longer of 20 years from the date of filing or 17 years from issuance of the patent.

The first thing which should be considered in determining whether a utility application should be filed is whether the subject matter of the invention is proper under the patent laws. One can address this issue by first considering what types of subject matter are not patentable. Non-patent subject matter includes:

1. Printed matter, where the invention resides solely within the printed matter and does not involve any mechanical features;

2. Naturally occurring articles, where there has been *no human intervention***;**

3. Methods of doing business, such as book-keeping and accounting techniques; and

4. Scientific principles, such as theories and formulas.

Utility patent protection is available for:

(*i*) processes (*i.e.,* methods);

(*ii*) machines;

(*iii*) articles of manufacture; and

(*iv*) compositions of matter.

Examples of process-type inventions that may be patented include chemical processes, such as the manufacture of chemicals, and methods of treating or diagnosing disease. Also included in the category are methods of using previously-known drugs. The terms "machines" and "articles of manufacture" should be fairly self-explanatory.

A. In biotechnology, some of the most valuable types of patents fall into the *composition of matter* category. The term "composition of matter" includes mixtures of chemicals, pure chemical compounds, polymers (such as plastics), and *purified products* not pure in nature. Examples of this latter category are antibiotics, enzymes, and lymphokines. More specifically, patents can be obtained for:

(*i*) DNA

(*ii*) proteins

(*iii*) antibodies (*e.g.,* monoclonal antibodies)

(*iv*) pure cultures of microorganisms and viruses

(*v*) transgenic plants and animals.

Assuming an invention is patentable in terms of subject matter, there then remain three statutory requirements which the invention must meet: the invention must be useful, novel, and non-obvious.

"Useful" means the invention must be of some (even if small) benefit. Thus, the statute precludes obtaining a patent on an invention which is merely a curiosity, or which is illegal or immoral. For example, a machine useful solely for producing counterfeit money is unpatentable.

The requirement that the invention be useful does **not** mean it must rise to the level of being *commercially* useful. Many inexperienced applicants believe they must delay filing a patent application until they have developed the invention to the point where it is a commercial product.

For example, where a new anti-cancer drug has been discovered, inventors sometime believe, wrongly, that human data meeting the requirements of the FDA must be obtained in order to file a patent application, whereas it is usually sufficient to have *in vitro* data showing inhibition of a cancer cell line. In fact, delaying filing a patent application in order to generate elaborate experimental results carries with it the very real risk that another inventor will file ahead of you.

Another statutory requirement of the patent law is that the invention be novel. The events which can prevent an invention from being considered novel are events which occur before the date of invention, and more than 12 months before the filing date of the patent application.

Thus, a patent cannot be obtained if, before the date of invention, the invention was: publicly known or used by others in this country, or patented or described in a printed publication anywhere in the world. Further, a patent cannot be obtained if, more than 12 months before the filing of the patent application, the invention was patented or described in a printed publication anywhere in the world, or in public use or on sale in this country.

It is important to keep in mind that the 12-month publication grace period is unique to U.S. law; most foreign countries have a different rule, known as *absolute novelty*. (Absolute novelty means patent protection is lost by sale or publication of the invention prior to the filing of the patent application).

Non-obviousness of an invention, like novelty, involves a comparison of the invention with the prior art. But, unlike novelty, which only considers prior art which is the same as the invention, obviousness considers the prior art with respect to what the next obvious step would have been. In evaluating obviousness, it is necessary to evaluate the so-called subjective and objective indicia of obviousness.

The subjective factors relating to obviousness have been defined by the U.S. Supreme Court: the scope and content of the prior art; the differences between the invention and the prior art; and the level of ordinary skill in the art.

The objective obviousness factors, developed by the courts over several decades, are: commercial success; long-felt need; failure of others; unexpected results; skepticism by others; and teaching away in the literature.

A patent application also must teach one of the ordinary skill in the field how to make and use the invention. This is known as the *enablement requirement*. If the patent application is so inexact as to require substantial experimentation for success, the invention may be unpatentable.

The patent statute also requires that the inventor disclose the *best mode* for making and using the invention. Thus, where an inventor has developed two different processes for synthesizing a compound, but one of the processes is less expensive or simpler, then the patent application must teach that preferred process.

B. In biotechnology, the enablement and best mode requirements have resulted in what has become known as the *deposit requirement.* When life forms are an essential part of a patent application, special problems arise with respect to satisfying the enablement requirement. Sometimes these types of inventions cannot be reproduced by following a written description. For example, new antibiotics made by microorganisms not generally available to the public raise the issue of whether merely describing the microorganisms, and where and how they were found, satisfies the enablement requirement. It was on this basis that the Patent Office established the policy of requiring inventors to place these rare organisms in depositories accessible to the public.

Investorship: Another issue which must be addressed when filing a patent application is that of inventorship. In the U.S., unlike many foreign countries, the patent application must be filed in the name of the true inventor or inventors.

Joint inventorship requires that each inventor contribute to the *conception* of the invention. Conception is the mental formulation of an idea complete enough so as to enable one of ordinary skill in the field to reduce the concept to practice without undue experimentation. Contribution to the actual reduction to practice is irrelevant for purposes of determining inventorship.

Although it is not necessary for joint inventors to physically work together, there must be some degree of collaboration among them. Further, an individual who merely follows the instructions of another is not a joint inventor. For example, a lab technician who carries out experiments under someone else's instructions and records the results is not an inventor. Finally, an individual does not become a joint inventor by suggesting a desirable end or result without suggesting the means of accomplishing the result.

I. Biotechnology has increased the availability of many natural biological products useful in treating various diseases. These products, such as human growth hormone (hGH), often exist in such minute quantities that isolation from natural sources is impractical or extremely expensive. Sometimes, such as in the case of insulin, the product can be isolated from alternative natural sources (*e.g.,* pig), but may be less effective or accompanied by undesired side effects.

II. Biotechnology has also been used in disease detection. For example, HIV diagnostic tests have been developed using recombinant DNA technology.

III. Biotechnology research is extremely risky and expensive and often involves time-consuming, resource-intensive characterization of the genes that encode the desired biological product. Sometimes, the product itself has to be characterized to determine which gene is the "right" one. Organizations who do biotechnology research are very interested in protecting their investment by obtaining patents to prevent others from freely practicing the "fruits" of this research.

    What "fruits" of biotechnology research can be patented? This list is almost endless. For example, patents can be (and have been) obtained on the isolated gene, modifications of the gene, purified and modified biological products encoded by the gene, methods for making the gene and its encoded products, as well as methods for using the gene and its encoded products.

    The ability to obtain patents on these "fruits" has been aided by the perception of biotechnology as an "unpredictable" art. One of the requirements for getting patent coverage is that the invention not be obvious to one of ordinary skill in the art. The perception of biotechnology as an unpredictable art tends to negate obviousness, as reflected in many court cases that have upheld the validity of biotechnology patents.

IV. As owners of biotechnology patents have unfortunately found out, the perception of biotechnology as unpredictable is a two-edged sword. To be valid, the patent must also contain a written description of the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art" to make and use the invention ("enablement requirement"). The predictability as to what will (and will not) work greatly determines how much of the patented invention is enabled.

    The enablement requirement has proven to be a significant barrier to enforcing broad biotechnology patents. Many broad biotechnology patents claim the invention in terms of its functional characteristics, rather than its chemical structure, to obtain broader coverage. For example, some biotechnology patents claim the gene in terms of its ability to encode a class of proteins that are functionally analogous to a particular biological protein. Other broad biotechnology patents claim the biological protein (*e.g.,* hormone) in terms of its activity.

These broad "functionalized" biotechnology patent claims have not faired well in court. The courts have applied a fairly stringent enablement standard to such broad claims because of the perceived unpredictability of biotechnology. This stringent standard has been difficult to satisfy, especially since the litigated patents usually have had only one or a few working examples of the gene or product.

The difficulty in satisfying the enablement requirement in the biotechnology area has led alternatively to claims limited to genes or encoded products that are specifically exemplified in the patent. However, as the litigated patents show, a competitor may slightly alter the gene or encoded product, and thus avoid infringing such narrow patent claims.

So how does one get broad biotechnology patent claims that will satisfy the enablement requirement? Here are some suggestions:

(*a*) Exemplify as much as possible in the patent disclosure the scope of the biotechnology being claimed. This includes how to make and how to use the claimed biotechnology. It is also important to understand as much as possible the operative limits of the claimed biotechnology and to put that knowledge into the patent disclosure. Be careful in relying on "illustrative" or "prophetic" examples without actually testing a representative selection of such examples to see if they do work. The litigated patents have shown the danger of relying on such examples when they later turn out not to work. Also, make sure each term, competent and step recited in the patent claim is defined in sufficient detail. As one 1996 court case painfully demonstrates, reliance on general teachings in the art can be extremely risky in the biotechnology area.

(*b*) Augment the initial patent disclosure by filing continuation or provisional patent applications to include new working examples or learnings. To preserve patent rights in "first to file" countries such as Europe, it is not unusual for a biotechnology patent to be filed with broad claims, but with only a few or possibly only one working example disclosed. Rather than rely on what later may be held to be inadequate enablement, consider filing continuation or provisional patent applications to include new working examples or learnings. Provisionals are especially valuable for doing multiple filings (at relatively low cost) to augment the initial patent disclosure. For example, five U.S. provisional applications can be filed for less than the cost of one traditional U.S. patent application.

(*c*) Where possible, pursue broad claims to methods for making the gene or biological product. Do not overlook the value getting patent coverage on the method of or making the gene or biological product. Under appropriate circumstances, importation of the gene, and more importantly the biological product, into the U.S. can be prevented if the gene or biological product is made by a patented method. Indeed, one court case that prevented importation of hGH made by a patented method involving recombinant DNA suggests broad method claims for making genes or biological products may be less likely to run afoul of the enablement requirement.

The perceived unpredictability of biotechnology has certainly made it more difficult to get enforceable broad claims on the "fruits" of biotechnology research. However, as the courts have made clear, broad patent coverage on these "fruits" is not precluded. The challenge is to craft patent disclosures that satisfy the more stringent enablement standard applied by the courts to the biotechnology area.

SPECIAL APPLICATION OF PATENTS IN BIOTECHNOLOGY

Examples from US

The Harvard mouse was the first patented transgenic animal

Some patents achieve their notoriety in the marketplace, others in the court room; the Harvard mouse grabbed headlines the day it was granted. This was the first patented transgenic animal, a mouse that contained genes from another species. These particular genes, called *oncogenes*, trigger cancer growth. By inserting them into a mouse, researchers can study the effects of cancer-fighting drugs and suspected carcinogens without human testing. Researchers can explore potential treatments — and cures — more effectively, and more safely than otherwise possible.

Harvard's patent was particularly broad, covering any non-human mammal that had an oncogene inserted. The discovery led other scientists to develop—and patent—their own transgenic animals, using all sorts of genes. Yet from day one, the patent, and the science behind it, have been extremely controversial. Some question whether people should have an

exclusive right to an animal — even a genetically altered one. Others argue that genetically altering nature is in itself troublesome.

Initially the Patent Office rejected the Harvard mouse application on the ground that animals were not a category of patentable subject matter, says Paul Clark, now a name partner at Boston's Clark & Labeling, who prosecuted the patent. Clark visited the examiner to argue against the decision, but to no avail. Shortly after that, however, Clark's luck changed. The Patent Office had approved a controversial patent on an oyster, lifting the ban on animals and saving the mouse.

In Canada, Harvard's mouse has been the subject of a decade-long legal battle, stemming from the Canadian Patent Office's refusal, in August 1993, to award it a patent, holding that the mouse was mainly the work of nature, not man. That decision was reversed by an appellate Court in August 2000, but the Canadian Supreme Court has agreed to hear the matter.

The polymerase chain reaction (PCR)

Think of the polymerase chain reaction as a Xerox machine for DNA. The process enables scientists to take a minute amount of genetic material and multiply it exponentially — increasing the sample millions of times over in just a few hours. It is the crucial process in fields like forensic research, where the material that scientists have at hand to work with — a strand of hair from a crime scene, for example, is, by itself, often insufficient for testing. "Before PCR, you were flat out of luck if you didn't have enough DNA," says Lisa Haile, an attorney at Gray Cary Ware and Freidenrich. "That's why it's only recently that you've seen [genetic testing] in court".

PCR's uses go far beyond DNA fingerprinting. The process has revolutionized drug research and medical diagnostics by enabling researchers to find faulty genes and identify viruses. It has also allowed scientists to map the human genome and ushered in the technology behind cloning.

PCR patents have also ushered in some lengthy litigation. The validity of Mullis' first two patents were challenged by E.I. du Pont de Nemours and Co. in 1990. The company contended that the PCR process was made obvious by the earlier work of H. Gobind Khorana, a professor at the Massachusetts Institute of Technology and a Nobel laureate. But in February 1991, a federal jury upheld the patents, finding that Khorana's work did not anticipate the PCR technology.

The bigger legal stir was caused by the 1989 patent, which covers the key Taq polymerase enzyme used to carry out PCR. Hoffman-La Roche, which had acquired the PCR patents in 1992 from Cetus Corps., sued Promega Corp. later that year for what it claimed was a breach of a licensing agreement. Promega countersued, questioning the validity of the Taq patent. In 1999 a San Francisco Federal Court found that Cetus had committed fraud by intentionally omitting material information from its patent application, and invalidated the patent. Hoffman-La Roche appealed to the U.S. Court of Appeals for the Federal Circuit, which held a hearing in May 2001, but has yet to make a ruling.

Hepatitis B

Hepatitis B is a killer. The infection leads to more than 1 million deaths a year, according to the World Health Organization, and is also the leading cause of liver cancer. In the United States, the hepatitis death rate has fallen to 5,000 deaths a year, largely because of an effective vaccine that has become a childhood inoculation in the past decade and a half.

The high-tech vaccine is the first produced using genetic engineering. Kenneth Murray's

patent one of several that have been crucial to conquering the disease, covers the so-called "intermediates" that are useful in the production of hepatitis B virus antigens. Intermediates are substances that trigger the production of disease-fighting proteins known as antibodies. By developing these antibodies prior to exposure, the body creates a defensive barrier, preventing hepatitis B infections. Prior to Murray's work the antigens were extremely hard to develop in the lab. By using genetic engineering techniques, Murray was able to create antigens in great quantities — paving the way for readily available vaccines, and for tools to detect hepatitis B infection.

Today every one of these vaccines implicates the patent – and puts licensing fees in Biogen's coffers (licensing rates are confidential). The global market for the hepatitis B vaccine now exceeds $1 billion a year, and is expected to grow as more countries adopt World Health Organization recommendations for the vaccination of newborns, teenagers, health-care workers, and other at-risk populations.

HIV protease inhibitors

Protease inhibitors aren't a cure for HIV infection, but they can keep the disease manageable — and have helped to drastically reduce the number of deaths from AIDS. Approved for use in 1995, the inhibitors have shown a remarkable ability to suppress HIV viral loads, particularly when taken in a "triple cocktail" with two other drugs called *reverse transcriptase inhibitors*. By inhibiting the virus's protease enzyme, the drugs prevent viral replication — in essence, holding the virus in check and keeping it from developing into full-blown AIDS. It didn't take long for these drugs to work their magic, either. In 1997 the number of AIDS-related deaths in the U.S. dropped by 47 per cent, according to the Food and Drug Administration.

Protease inhibitors have also called attention to a major criticism of the patentability of life-saving drugs. Manufacturers, using patents, can set prices so high the drugs cannot be obtained by many of the people who need them. Merck's Crixivan, the most widely used protease inhibitor, costs over $6,000 a year in the United States. But the vast majority of HIV-infected individuals live in the World's most impoverished nations, particularly in Southern Africa, where over 250,000 people died of AIDS in 2000.

Under pressure to provide greater access to medication, Merck announced last year that it would cut the price of Crixivan in developing nations to $600 a year — a level, the company says, at which it will make no profit. But even that price is too high for most patients, who must rely on charities and relief groups to buy the drugs for them.

Primate embryonic stem cells

Embryonic stem cells are as undecided as a college freshman. They can become heart muscle, bone, skin — virtually any type of human tissue. But stem cells pick their major petty quickly: roughly a week after an embryo is created. James Thomson's breakthrough was in finding a way to isolate and maintain stem cells to keep them from differentiating. Thomson's cells can reproduce indefinitely in the laboratory, producing a omitless supply.

The potential is enormous. By figuring out how to direct their differentiation, researchers can help stem cells become blood cell to boost dwindling supplies, skin to replace that just by burn victims, or heart muscle damaged by disease. Specialized cells can also enable drug researchers to screen new compounds more quickly. Research in these areas is well under way. The stem cell controversy has been enormous, too. Many worry that cells may come from aborted embryos, or from embryos produced for the sole purpose of harvesting them. Swayed by the

potential of stem cell research, the Bush administration lifted the ban on federal funding for stem cells last year for a limited number of stem cell lines.

It was the lack of funding that led Thomson, a University of Wisconsin researcher, to seek private support for his work. The source of those funds – biotechnology company Geron Corp. — later obtained an exclusive license to six cells types created from Thomson's research. But after Bush's announcement, the Wisconsin Alumni Research Foundation (WARF), which held the patent, worried that Geron could stifle the flood of competing research the new federal funding would enable. In August 2001, WARF filed suit to take back, or at least limit, Geron's exclusivity. The two parties settled in January 2002. Geron relinquished exclusivity in three of the six cell types, and agreed to nonexclusive rights on any future cell types, thus paving the way for more research by other scientists.

Examples from India

Patenting in drugs, filings by Indians/Indian companies

Indian scientists and technologists have been quick in responding to the post TRIPS challenge by filing substantially more patent applications. The filing by Indians has gone up by 155% over the applications published in 1996 as compared to an increase of 25% in the filing by foreigners/foreign companies. However, the former is now about 33% of the latter as against 16% observed in the earlier analysis, a significant improvement to be noted. Further, now there are seven companies/institutions which have filed 5 or more applications as against two observed in the preceding analysis, showing a growth of about 250%. It has been noted that almost 30% of the applications relate to herbal and ayurvedic medicines; such applications have even been filed by companies like Lupin and JB Chemicals. However, this is only the beginning of a triumphant journey, a successful end will be determined by how many of these are finally accepted and how many of these are picked up for commercialization. A good beginning portends good results.

Of the Indian applications filed, 114 applications were filed by Indian companies and the rest 52 by individuals. CSIR with 19 patent applications, ranks first among Indian companies and enjoys an overall 8th position jointly with Merck Patent. The CSIR applications relate to inventions for processes producing the following: oxindole as intermediate for producing the tenidap, an anti-inflammatory agent, analgesic analogous to enkephalin, vaginal contraceptive, 17-ketosteroids, dihydroasperoside and dihudrosiredloside, artmesnin, antibiotic from fermented froths, ciprofloxacin, organotin useful as cytotoxic agents, L-alanyl-l lysyl derivatives useful as antiasthmatic/antiallergic, pyridines as potent cardiovascular agents, codeinone, chloropropane and 2-piperidone useful as potential hypotensive agents, pyridine and 3-picoline, lipopolysaccharide (LPS), 7 methoxy deoxyvasicinone, 4-arylamino/alkylamino-4-demethylpodophyllotoxins as potential anticancer agents: and epichloromydrin. Three of the **Lupin's** applications concern anti-tubercular composition. Other applications include process for purification of atenolol (2-4-hydroxy-3-1) phenyl acetamide, process for extraction of hydroxycitric acid from fruit and garcinia species, process for the manufacture of ceftazidime, process for isomerization of N-7 isomer to N-9 isomer, process for the manufacture of 3-hydroxy-3-cephem derivatives, process for manufacture of cephalosporin antibiotics such as cefazolin, a regiospecific process for synthesis of acyclic nucleosides and ayurvedic formulation from *Amla* and *Ritha.* **Neam Herbal Remedies** has focused on pre-cooked ayurvedic medicinal food and all the applications fall in this area. The applications from **Dr. Reddy's Foundation** relate to new heterocyclic compounds having antidiabetic, hypolipidaemic, antihypertensive properties, their preparation and pharmaceutical compositions containing them; benximidazole derivatives as antiulcer agents; novel heterocyclic compounds for treating dia-

betics and related problems; 4-hydroxy-10-deacetylbaccatin III derivatives; azolidinediones useful for the treatment of diabetes dyslipidemia and hypertension; podophyllotoxin analogues and their derivatives as anti-cancer and anti-viral agents. Applications filed by Hindustan Lever are not included under the Indian companies as all of these are convention applications.

All the seven applications filed by the Indian citizens, **P.B. Mathur** et al, are ayurvedic medicines for reducing cholesterol and treating chronic diseases such as cough, acidity and gastritis, piles, sinusitis, and cold. Two of the **Sun Pharmaceuticals'** applications relate to antihypertensive fixed-dose combination products while the other two are on topical antibacterial anaesthetic combinations. The remaining two applications are entitled 'a process for the recovery of tramadol as cis-hydrochloride in asymptotically quantitative amount from mixtures of diastereomers of tramadol' and 'an improved process for the preparation of 1-(2,3-epoxypropyl)-5-nitroimidazole'.

A few other Indian companies and institutions who have filed more than one application with the no. of applications filed given in brackets are Panacea Biotech (4), Ranbaxy Laboratories (4), Raptakos Brett & Co. (4), Tablets (India) Ltd. (4), National Institute of Immunology (3), Osmania University (3), Dabur Research Foundation (2), Hindustan Antibiotics (2), IIT (2), Sonic Biochem Extraction Pvt. Ltd. (2), Sree Chitra Tirunal Institute for Medical Science and Technology (2), and Themis Chemicals (2).

PATENTING OF LIVING ORGANISMS

Patenting Life? — An Introduction to the Issues

Once upon a time, we knew that animals were products of nature. We used them and "owned" them, but it was different from owning a pair of shoes. Animals could get up and walk away; shoes couldn't. And unlike patent leather, you couldn't patent a cow. Patents are about inventions, and since when had human beings invented an animal?

Since 1984, if you believe Harvard University and the US Patent Office. For that was when Harvard applied for a patent on a genetically modified mouse, which was granted 4 years later, causing a big bang of controversy which soon reached the shores of Europe and whose ripples are still very much in evidence. For this was the first time it was officially decreed that an animal could indeed be classed as an invention. Moreover, it was a mouse specifically engineered to have an increased probability of suffering malignant tumours — for use as a "model" for studying human cancers and carcinogens.

Controversy in Europe

The combination of these two factors has raised human hackles far and wide. It generates surprisingly heated arguments wherever the issue is debated. The question of patenting "animate matter" has given long term headaches to the European Patent Office in Munich, and in March 1995, it led to the first ever rejection by the European Parliament of a European Commission Directive. A new draft EC Directive on patenting is currently being discussed in the early committee stages of the European Parliament, and is again the subject of deep seated controversy between industry proponents and many diverse groups which include church groups, NGO's, environmental and animal welfare organisations, and also many doctors, farmers and ethicists.

Biotechnological Inventions — Products of Nature or Products of Industry?

You cannot patent a mere discovery. It must have a non-obvious "inventive step", and some specified practical application. Patent law was framed in an industrial context, and typi-

cally applied to objects, chemicals, designs and processes. Agriculture was seen as lying outside this realm. You could patent a mouse trap, but not a mouse. But, with the rise of biotechnology, a shift has occurred, partly in technical sense, and partly in our perceptions.

Once it became possible to alter the genetic make up of living things, researchers could genuinely claim an "inventive step" in the organism itself. And since such research is expensive and easily copied, organisations wanted to patenting genetically modified organisms to protect their valuable investment. The key case concerned a micro-organism, perhaps only a small step from patenting biochemical products. It went right up to the US Supreme Court, who in 1980 ruled that "anything under the sun that is made by man" was patentable subject matter, which turned it into the giant leap which has set the trend ever since. But it was not until its implications began to extend from micro-organisms to warm and furry animals that the fundamental question dawned on people generally: were they right?

Oncomice, transgenic sheep, or whatever: should we be patenting our fellow creatures at all? Isn't this violating something rather basic in our attitudes to nature, implying they are nothing more than machines for our use? We say we "own" animals, but what does this really mean? They have their own lives and freedom which we are surely to respect – simply as parts of nature alongside us, and, from a Christian perspective, as God's creatures each of inherent worth. For many, the heart of the problem is that to patent an animal includes it in the same category as mere mechanical objects. Is that symbolic association sending ourselves and our society entirely the wrong kind of signal? Patent expert Stephen Crespi suggests that living things are now regarded as "products of manufacture" and agriculture to be a kind of industry. If this is true, is this a shift in perception we should be counteracting?

Patenting the Human Genome—Losing Investments or Losing our Humanity?

We are not just talking about animals and plants. Sections of the human genome are being identified by the thousand. Should these be patentable, if you could prove they weren't just "discoveries"? Many US researchers with an eye to the main chance thought "yes"? The subsequent transatlantic scramble to grab the richest pickings from the Human Genome Project has demonstrated that once one player starts protecting, it puts everyone else under pressure to follow suit. Dubious and torturous arguments are posed to try to prove that a copied human gene is not a discovery. But these obscure the basic question — is the patenting of sections of the human genome simply an abuse of human dignity, under the guise of commercial enterprise?

Alternatively, is the controversy a storm in a tea cup, as much of the biotechnology industry maintains, a storm threatening its competitive prospects and the very fibre of its work? If they cannot patent, it is claimed, then no one will invest the large sums of capital needed for genetic research, or it will all simply be kept secret. Advances in science, medicine and agriculture will be curtailed, information will not be shared. Avoidable suffering will go unallieviated and economic opportunities lost to other nations who aren't so fussy about non-issues. Against these powerful arguments, who would stand in the way? Well ... quite a lot of people, it would seem.

If animals or our own genes are products of nature then we cannot claim invention. If they are nothing more than products of industry then I believe we are losing something of our humanity by putting them in the same box as widgets. If they are both, however, then perhaps we need a new system of intellectual property involving living material, instead of shoring up a patenting system which was manifestly not designed for such cases. Much depends on what we need to patent. There is a good case for a pharmaceutical company gaining a patent on, say, the use of a section of the human genome to produce a particular therapeutic drug. But it is a very

different matter if the same company claims a patent on the sequence itself, for any use whatsoever, just by virtue of having invested a lot of money in isolating it and having identified its function in the body. To many people, that is one step too far, and is claiming more than is justified, for what is still only a discovery, not a true invention. It is also feared it could actually hamper research and delay vital discoveries, by putting off other companies from investing in other potential therapeutic uses of the same gene.

There is also the moral dimension. Many people would also say that knowledge of a genetic sequence itself is part of the global commons and should be for all to benefit from. To patent parts of the human genome as such, even in the form of "copy genes", would be ethically unacceptable to many in Europe. In response it is argued that patenting is the legal assessment of patent claims, and should not be confused with ethics. But patenting is already an ethical activity, firstly in that it expresses a certain set of ethical values of our society; it is a response to a question of justice, to prevent unfair exploitation of inventions. Secondly a clause excluding inventions "contrary to public order and decency" is part of most European patent legislation — an extreme case of something like a letter bomb would be excluded as immoral. But now we have brought cancerous mice and human genetic material in the potential frame of intellectual property, ethics has moved to a much more central position, where it sits uncomfortably with the patenting profession. They do not like the role of ethical adjudicator to be thrust upon them by society. And they have a point. Patenting is probably the wrong place for society to be deciding once and for all the morality of, say, the oncomouse. But this only points to a serious anomaly in the way we assess biotechnology.

Four Main Issues

(*a*) What is a patent, and why is it so important in biotechnology?

(*b*) Should we allow patents on living organisms and human genes?

(*c*) When does a discovery become a human invention?

(*d*) How do we decide what is ethical in biotechnology?

(*a*) What is a patent, and why is it important?

A patent is granted to someone who invents something novel which has an industrial use. Its purpose is to prevent other people from marketing it without paying royalties to the inventor. It lasts 20 years to allow a fair return on the inventor's investment, on condition that the full details are published. It does not give the inventor the right to make the invention (that is subject to other regulations) but it stops others doing so. It must be something novel, not an obvious extension of present knowledge, and you cannot patent a mere discovery. It has to have a practical use. The patent system has evolved over centuries around products of industry like mechanical inventions or chemical processes.

Up to about 1980, products of nature were normally excluded. You couldn't patent a plant, say. But once biotechnology began to discover ways of modifying living organisms, first bacteria and then plants and animals, pressure mounted to allow patents on these. Genetic research is expensive and it often takes years from discovery to market. In a competitive world, companies say they have a legitimate need to know they have a chance to protect their large research investment with a patent. The question is how far should this be taken? The EU Directive has aroused widespread criticism that it has bowed to the demands of industry to the point that basic public values were simply overridden.

(*b*) Should we allow patents on living organisms?

To get a patent you have to have invented something. Can humans claim to have invented

a genetically modified animal or plant, just because they have added one or two genes to it? For the church this would make an unwarranted claim to have invented something which is part of God's creation, or a product of nature. What have we really invented is not the animal but the new sequence. Underlying this is an important insight. To extend patenting from industrial artefacts to living things in themselves is to violate a normal ethical distinction between what is alive and what is not. They are not just another industrial commodity. Christian moral principles stress the idea of relationship and care for nature as more important than a purely functional view of industrial utility. The relationship with life takes precedence. So we may patent a mouse trap, or a novel gene sequence used in a mouse, but not a genetically modified mouse itself, and so also for other animals and plants.

(*c*) Should we allow patents on human genes?

One of the hottest issue is whether we might patent the knowledge of a human genetic sequence. In normal understanding this is a discovery, and so should be unpatentable. Patents are not allowed on human body parts, so why patent genes, which are just as much part of our human make up? But according to the EU patent directive, even a human gene becomes a patentable invention because you have to copy it millions of times in order to analyse it, so the resulting "copy genes" are inventions. Quite apart from the ethical objections, many scientists dispute the logic of this, because the key thing is the *information* encoded in the gene. By definition that is a discovery. Also the act of gene copying is not novel but a standard technique. The EU has turned a deaf ear to these and other arguments, but the Directive is now being challenged in the European Court by the Dutch Government.

An added concern is that patenting genetic discoveries implies an attitude of "winner takes all" over knowledge which could address areas of acute human suffering. It has led to undignified scrambles to claim commercial priority over discovering genes, and has not always encouraged the spread of medical research or investment. It may even add to the cost of therapies. The church considers it unacceptable to claim invention over genes as part of our human make up. Investment in medical research will be adequately ensured by allowing patents on the application of a human gene to make a specified range of pharmaceutical products, without needing to patent the gene itself or all its uses.

(*d*) When does a discovery become a human invention?

One company has claimed that human DNA is patentable because the intellectual effort to discover it raises it from a discovery to an invention. To many, this is a case of special pleading which would abuse the very idea of patenting, since *all* discoveries require intellectual effort. Logically, this would bring an end to the notion of discovery and mean that anything could become a commodity.

(*e*) How do we decide what is ethical in biotechnology?

Some say ethics has no place in patenting. Yet every activity involving law also involves ethics, and the EC official advisors on bioethics have said that once animate matter is involved, ethics becomes a prominent issue in patenting. But this raises a serious question about how our society should assess the progress of biotechnology. Often the first time the public hear about a biotechnological invention is when the patent is published. Up to this point, it is secret. And because a patent gives no right to market the invention, it isn't (at least in theory) a judgement about ethics, either way. The problem is that no proper system exists, either in Europe or the UK, which allows for an ethical assessment to be made of a biotechnological invention, while its patent is being assessed, to enable society to decide whether it wants it to be marketed or not. This serious deficiency urgently needs to be addressed, if this vital area of science is to remain accountable to the public and not driven by commercial interests alone.

What are Plant Breeder's Rights?

Plant Breeder's Rights are exclusive commercial rights to a registered variety. The rights are a form of intellectual property, like patents and copyright, and are administered under the *Plant Breeder's Rights Act 1994* (the Act). The rights are applied for using application forms available from the Plant Breeder's Rights Office. In relation to propagating material of the registered variety, successful applicants have exclusive rights to

(*a*) produce or reproduce the material;

(*b*) condition the material for the purpose of propagation (conditioning includes cleaning, coating, sorting, packaging and grading);

(*c*) offer the material for sale;

(*d*) sell the material;

(*e*) import the material;

(*f*) export the material; and

(*g*) stock the material for any of the purposes described in (*a*) to (*f*).

In certain circumstances, principally if the breeder has not had a reasonable opportunity to exercise the right on the propagating material, PBR extends to harvested material and, subject to a similar set of qualifications, to products obtained from harvested material. Exceptions to the breeder's right are the use of the variety privately and for non-commercial purposes, for experimental purposes, and for breeding other plant varieties. A variety can be used for these purposes irrespective of the existence of Plant Breeder's Rights. Farm saved seed is permitted, unless the crop is declared by regulation to be one to which farm saved seed does not apply. Currently no crops have been declared in this way.

Who can Apply for Plant Breeder's Rights?

Applications are accepted from the original breeder of a new variety (from their employer if the breeder is an employee of an organisation) or from a person who has acquired ownership rights from the original breeder. Overseas Breeder's or owners must appoint an agent to represent their interest in Australia.

Eligibility for Registration

Only new or recently exploited varieties can be registered. A new variety is one which has not been sold with the breeder's consent. A recently exploited variety is one which has been sold with the breeder's consent for up to 12 months in Australia and for overseas varieties this limit is up to four years (with the exception of trees and vines in which a six year overseas prior sale limit is permitted). To be eligible for protection, the applicant must show that the new variety is distinct, uniform and stable. To obtain acceptance of an application and provisional protection it must be established that there is a prima *facie case* that the variety is distinct from all other varieties of common knowledge. To obtain a grant of PBR the applicants must verify these claims normally by conducting a comparative test growing which includes the new variety and the most similar varieties of common knowledge.

Steps in Applying for Plant Breeder's Rights

- Obtain from the breeder a signed Authorisation to act as their agent in Australia for the variety in question if your role is as the Australian agent of an overseas breeder.
- Complete Part 1 of the application form, supplying a photograph of the new variety, paying the application fee, nominating an accredited 'Qualified Person' and, if the variety is an Australian species, despatch as soon as possible a herbarium specimen;

- Engage the services of the nominated accredited 'Qualified Person' to plan and supervise the comparative growing trial;
- Conduct a comparative growing trail to demonstrate Distinctness, Uniformity and Stability (DUS), complete Part 2 of the application form and paying the examination fee;
- Deposit propagating material in a Genetic Resources Centre.
- Examination of the application by the PBR Office, which may include a field examination of the comparative growing trial; and including
- Publication of a description and photograph comparing the new variety with similar varieties in Plant Varieties Journal, followed by a six-month period for objection or comment.
- Upon successful completion of all the requirements, resolution of objections (if any) and payment of certificate fee, the applicant(s) receive a Certificate of Plant Breeder's Rights.

New Legislation—the Plant Breeder's Rights Act 1994

To conform with the 1991 revision of the International Convention for the Protection of New Varieties of Plants (the UPOV Convention), the Australian Parliament has passed new legislation, the *Plant Breeder's Rights Act 1994*, replacing the *Plant Variety Rights Act 1987*, which has been repealed. The principal changes are:

- In tree and vine varieties, PBR continues for 25 years from the date of granting, and in all other varieties, for 20 years from the date of granting;
- Sale in Australia with the breeder's consent will be permitted for up to one year prior to applying for PBR;
- Sale overseas with the breeder's consent will be permitted in tree and vine varieties for up to six years and in all other varieties for up to four years prior to applying for PBR;
- Farm saved seed will continue to be allowed, unless the crop is one declared by regulation to be one to which farm saved seed does not apply;
- Intentional infringement of a breeder's rights attracts a penalty of $55,000 for individuals and the penalty for corporations is potentially five times greater, *i.e.,* $275,000;
- Breeder's are deterred from taking unfair advantage of other Breeder's efforts by the introduction of the concept of the Essentially Derived Variety (EDV). A breeder who believes such a situation has occurred is able to apply to the office to have the second variety, declared an essentially derived variety;
- Transgenic plants, algae and fungi can be protected;
- Plant Variety Rights granted under the old Act are treated as if they had been granted PBR; and
- Applications made under the old Act, but not finalised, are dealt with under the provisions of the old Act as if that Act were still in force.

Under the *Plant Breeder's Rights Act 1994*, both name and synonym of a plant variety are protected. A synonym is an additional name which the applicant may also use to commercialise the variety in Australia. However, acceptable variety name and synonym must comply with Section 27 of the Act and the *International Code of Nomenclature for Cultivated Plants 1995* (ICNCP 1995). For the purpose of this article a reference to a name is also a reference to a synonym.

Proposing a new and original name for a plant variety is not an easy task. It requires a bit of thought and accordingly breeders are frustrated when they can not get the name they want. Here are some simple rules which will help you:

Novelty

Before coining a name for a variety, make sure your proposed name is unique and it cannot be confused either in spelling or pronunciation with another existing one. (ICNCP 1995).

Length

The name should not have more than 10 syllables and no more than 30 characters, excluding spaces and single quotation marks. (ICNCP 1995).

Merit

The name could not be interpreted, as being likely to exaggerate the merits of the cultivar (like 'Best Ever' 'The Greatest', Tastiest of All') also it should not only be made up of simple descriptive words. (*e.g.,* 'Red', Giant White', 'Small'). (ICNCP 1995).

Punctuation

Do not use any punctuation marks except for an apostrophe, comma, a single exclamation mark, hyphen or full-stop. (ICNCP 1995).

Banned words

Certain words (or their equivalents in any language) are banned words and they cannot be used in the name, these are: cross, hybrid, grex, group, form, maintenance, mutant, seedling, selection, sport, strain, variety (or the plural form of these words in any language) or the words 'improved' or 'transformed' (ICNCP 1995).

Genus and common name

If your name is a single word, make sure that the word is not the same as that of a genus, whether in botanical, Latin or in a modern language. Erica, Daphne, Iris and Veronica happen to be Latin names of genera and are not permitted as cultivar names even though they are personal names as well. Similarly, Rose and Violet are common names of the genera and they too are not permitted. However, such a word may be used in a name of two or more words provided that it does not form the final word ('Erica Smith', 'Iris Jones' and 'Rosa Queen' are acceptable but 'Queen Rose' is not acceptable) (ICNCP 1995).

Also make sure that your name does not contain the botanical or common name of its genus or the common name of any species in that genus. ('Rosa Christmas Rose', 'Potato Jim's Spud' and 'Primula White Cowslip' are not acceptable) (ICNCP 1995).

Name of natural person or organisation

When the name consists of a name of a natural person living at the time of the application a written consent to the name of the variety will be required from that person. If that person is deceased within (10) years before the application was lodged then a written consent will be required from the legal representative of that person. If the name consists of a name of a corporation or other organisation, then a written consent will be required from the organisation.

UPOV name

If previously filed overseas, the denomination used in the first filing in a UPOV member country should be the official registered name in Australia (if not already in common use in Australia within the same denomination class or a Trade Mark in Australia in respect of live plants, plant cells and plant tissues). This requirement ensures that the variety is known by the

same name worldwide. If you intend to market the variety under another commercial name, a name that is not the UPOV name, include that name in the synonym.

If you have any confusion about a proposed variety name you are advised to contact the PBR office to check for the acceptability of the name before lodging an application. Examiners in the PBR office will assist you in this regard. You are strongly advised to wait until your proposed name has been accepted by this office before having pot/bag labels and promotional materials printed. You are also suggested to complete a form DEN 12/95 (Proposed Variety Names) with the Part 1 application to avoid processing delays relating to variety names and synonyms. If you are unsure of naming the variety at the time of the application, you can provide a temporary code name. You may change the code name at any time before the final granting of PBR by proposing a new acceptable name and paying a variation fee.

BIOETHICS IN BIODIVERSITY

Various forms of life say micro-organisms, plant and animal diversity have played a significant role in the making and maintenance of different systems and sub-systems. Since the appearance of modern man on the mother earth, vast changes have occurred in the biosphere mainly during an attempt for the fulfillment of the needs of human civilization from prehistoric times to date. There is no doubt that humankind has always tried to tame Nature in many ways to conquer it for establishing his supremacy on this planet. During this process while handling the abiotic and biotic environment, humans have created unimaginative chaos perhaps due to ignorance of ethics/bioethics. The demographic pressure on all sorts of natural sources/resources continuously went on increasing since stone age to the present day so called modern age of Science and Technology. Evolutionary speaking, in spite of the fact that humans who are highly evolved, could not avoid their own population explosion through their talent, advanced expertise and knowledge. Besides, this also led to the erosion of moral, social and scientific values which comprise bioethics, essential for bio-friendly development of human civilization.

Amongst other natural resources, biodiversity is perhaps hard hit where all norms and ethics have been found to be ignored and flouted by man for the attainment of his varied selfish interests. Globally, India ranks tenth in terms of species richness. Owing to this, many of its biodiverse forms, particularly unique animal diversity is being exploited for trade unethically. This immoral practice in the face of enforcement of certain National Acts such as The Wildlife (Protection) Act 1972, The Environment (Protection) Act 1986, The Indian Forest Act 1927 and the Prevention of Cruelty to Animals Act 1960, is to be highly condemned. Even the restrictions imposed through CITIES and TRAFFIC international failed to show expected results as human greed is surpassing all limits of decency and bioethics in biodiversity. In addition to violation of bioethics, authors, however, also feel that some unwanted restrictions and trade pose a serious threat to genuine field workers.

In zoological disciplines, the International Code of Zoological Nomenclature 1985, has Appendix 'A' which underlines the need of handling animal diversity through "code of ethics". Every now and then, one finds the ethics being ignored by biosystematists, as well. Should collection of live research material (biota) other than the one for which one is funded amount to violation of bioethics? Besides information on vertebrates, the authors would like to pin point some specific examples of butterflies, where who should follow ethics for sustainable use of these insects in the conservation and understanding of biodiversity, both specifically and in general. Until a bioethical approach is not given due recognition in scientific temperament while dealing biodiversity and its environment, the future of planet earth on this account seems to be dismal.

Humankind and Religion

K.K. Verma and Rashmi Saxena

Professor Zoology, HIG 1/327, Housing Board Colony, Borsi, Durg-491 001

Abstract

Religion is a characteristic of humankind. Nothing comparable to it is known in any other animal species. Religion is universal; every human population and tribe practices some sort of religion. Religion has acted as a very strong cohesive as well as divisive force. Much of turmoil in human history has been due to religion. Understanding and rationalizing religion is likely to be beneficial to us.

Essentials of all established and organized religions include two components, ethical and spiritual. The ethical part consists of what may be called social laws. Such laws are necessary for a healthy and progressive society. The notions of "hell" and "heaven" and of "punishment" and "reward" are perhaps meant to ensure adherence to the laws. The ethical parts of different religions include quite similar basic principles. The spiritual part is concerned with realization and worship of a Super Power. Though about form and abode of God and about rituals in worship different religions differ widely, realization of the situation, that all religions through their spiritual component tend to provide humankind with a support to fight their fears, will take us to infer that in this component too all religions are similar. Thus, all organized religions have much in common.

While universal monotheism is gradually gaining acceptance with spread of education and rationality, arrival of atheism or social religion, in our opinion, is not to come in foreseeable future, as humankind, in spite of all scientific development, still has fears to live with.

Hinduism, an ancient religion, has long been evolving. It includes magical rites, polytheism as well as monotheism. An advantage of this situation: a person, with whatever natural aptitude or cultural level, finds a suitable "niche" for his solace in the broad structure of this religion.

Old religious rituals make life interesting, and they should be retained. But those rituals, which are damaging to our environment, should be given up or replaced with less damaging practices.

Often here is bad mix-up of science and religion. It should be avoided, and it should be clearly understood that the approaches of the two are quite different.

Need for the Development of Social and Spiritual Ethics

Abstract

Social ethics includes such acts of prevention or minimization of cruelty to animals or otherhuman beings. To cite few examples:

1. Peeling off the skin of live snakes for commercial purposes.
2. Beating the animals to undergo training for a circus (Russian circus indicating human dominance).
3. Eating live animals bit by bit (Japanese restaurants with Sepia).
4. Close-up shots of prey and predator (International TV Channels).
5. Wild dogs chasing bulls and eating part after part.
6. Drinking blood from live bulls for developing strength (Africa).

7. Hunting animals after chase (Hunting sport) for food and pleasure.
8. Horses chasing the bullocks and causing humiliation (Spain Bull fight).
9. Sathi yagna as seen in Rajasthan of India.
10. Female feticide.
11. Ragging in schools and colleges to the extent of death.
12. Animals used for human sexual satisfaction.
13. Child labour and cruelty to children.
14. Spouse relationship.
15. Violence in Karate fight.
16. Making money from body show.

Regarding Spiritual Ethics, there are several practices, existing all over the world, that cause pain and agony. To cite a few examples:

1. Hatha yogis sitting on needles and thorns.
2. Lambika yogis elongating their tongues.
3. Piercing the tongue with rods and putting nails.
4. Rolling on pathways of young and married. Kneeling and walking sometimes over the staircase to appease gods.
5. Sri Kali with horror face exhibiting a cut head.
6. Exhibition of "taking out of intestine".
7. Exhibiting lingams with bleeding mouth.

Such antisocial and cruel acts performing openly before the audience consisting of elders, youngsters, school children and babies will cause pain and disgust and as such they may be discouraged as far as possible. Ethical knowledge should promote the quality of life.

ETHICS OF RESOURCE MANAGEMENT

Whether we intend to go through the 21st century or not, I am sure the 21st century will go forward leaving us behind and I do not know in what condition! It is in the fitness of things that we embark on discussing the techniques of resource management after delving deep into such issues as ocean futures, the environment and energy. I shall not, therefore, dilate on the problems that we face. However, in the process of squarely facing and solving some of our problems, if not all, we have an uphill task when it comes to management of our resources. No wonder, that in due recognition of the importance and relevance of management in the modern world, schools of management are becoming increasingly popular. But then we have to ponder whether or not the concept and practice of management as it is in vogue today, is suited for solving the problems that confront us now and are expected to in the near future.

It is true that the kind of problems that confront the developed countries are vastly different from the nature of the problems that confront Third World countries. Our task primarily is that of removal of poverty, ignorance, disease, and the consequent despair. Hence, the techniques of resource management appropriate to conducting the business of modern society where the despair is less marked, may not be appropriate to the Third World countries. If I can go into the heart of the matter, what we need are the techniques appropriate to the management of welfare, of innovation and management of our meager resources, to provide for the minimum needs of the maximum number of people. This is no ordinary task as it appears to my mind.

What have we done towards achieving our objectives in the past? This is the appropriate time to take stock and look ahead. We have inherited as a historical legacy a managerial system that was most suitable to subservient colonial interests. I am afraid, we have not changed much in this system with a view to modifying the same to suit the needs of welfare management. I do agree that we have been attempting a tinkering job here and there and nothing beyond. If we have to see that the personnel with the right knowledge and skills are entrusted with this onerous task. Then it is high time we examined our priorities and appropriate managerial techniques required.

I do not intend to go into some of the biological roots of human welfare in order to understand the process thoroughly. I can do no better than commend that wonderful book "small is beautiful" written by Schumacher in the early seventies. I do not know how many of you have pondered over the significance of the title. "A study of economics as if people mattered". As a biologist, to me this title was at once fascinating and inspiring. Here was an economist trained in traditional economics who thought deeply about the implications and assumptions and theories of economics affecting the people. In this book, he expounds the relevance of Buddhist economics wherein the keynote is simplicity and nonviolence. However, as per the modern trade and economic conceptions the one who consumes more is better off than a person who consumes less. This essential aggression is landing us in trouble. Beyond the consumption levels, all human activity is directed towards something thought of as good. So unless the primary problem of consumption has been sorted out and coordinated, our manifold urges, impulses and desires in striving for good is likely to be confused, contradictory, self-defeating and probably highly destructive. We have to create for ourselves an orderly system of ideas about ourselves and the world which can regulate the direction of our various strivings. As Schumacher puts it, "the true problems of living in politics, economics, education, marriage, are always of problems of overcoming and reconciling opposites". He elaborates further that, "education which fails to clarify our central convictions is mere training or indulgence. For it is our central convictions that are in disorder and as long as the present antimetaphysical temper persists, the disorder will grow worse".

This takes as to yet another useful concept of collective choice and social welfare as propounded by Sen. While collective choice is a crucial aspect of economics, notably of welfare economics, planning theory and public economics, the subject relates closely to political science in particular to the theory of decision-making procedure. It also has important philosophical aspects related to ethics and especially to the theory of justice. Thus, we slowly grope our way from economics to sociobiology.

The approach of the sociobiologist is highly congenial in fact, to the economists' since the both rely on competition, allocation of limited resource of say food and energy, efficient adaptation to the environment and other concepts also used by the economist. The trouble with sociobiologists however, is that they rely solely on the rationality related to genetic selection — the physical and social environment discourages ill-suited behavior and encourages better suited behavior. Economists, have on the other hand relied solely on individual rationality and have not incorporated effects of genetic selection. In this context, it should be understood that the central problem of sociobiology, namely the biological selection of altruistic behavior and an individual level is compatible and reconcilable with the modern economic approach. The reason why I went into this theoretical projection of economics and sociobiology are to see the extent to which they are related to the techniques of management must be firmly anchored to the individual's welfare as well as to the welfare of society as a whole. As Julian Huxley made it very clear, the forces of evolution in the case of Homo sapiens are overwhelmingly tilted in

favour of psycho-social development rather than biological growth. Spree Rogers S went a step ahead in contending that we have to bear in mind human conscious psychic mental forces, while dealing with human nature and human welfare.

Hence, there is need to recognize the imperatives before we incorporate it into the science of management for the future. These imperatives as they appear to us, are therefore, knowledge and understanding of human behaviour and concern for that central conviction namely the wisdom born out of good education which should ultimately humanize our social environment. We need to guard ourselves against slipping into a faceless dehumanizing and unstable industrial society. How can we achieve this? We have to pay increased attention to human values in the process of economic development and resource management.

This leads us necessarily to the need to adopt an organic system of management in preference to mechanistic systems. As was recognized by the management experts, a mechanistic management system is appropriate to stable conditions whereas an organic form is appropriate to changing conditions. The mechanist system of management is characterized by the hierarchic structure of control, authority and communication whereas the organic form is characterized by a network of structure of control, authority and communication. This applies to all levels of management whether local or central. This applies equally well to institutions as well as to our large sociopolitical systems of management and decision making. This also presupposes the adaptation of smaller and much more efficiently manageable infrastructural setup. It is also necessary that after imparting the required knowledge about the philosophy of the management of innovation for change through organic systems, we also give necessary training to the personnel involved in such branches of corollary disciplines as human biology, sociology, and sociopolitical sciences.

I do think that biologists have a special role to play in this regard in spreading the message that after all altruism has its firm biological roots and served the human race extremely well in raising his life span from 27 during the Neanderthal age to 72 at the present time. Psychosocial and psychobiological studies have proved beyond doubt that the female of Homo Sapiens tends to be more altruistic and reticent in order to be delivered of the baby through a painful process and to bring up the helpless infant over several years through parental care and love. Cognizance of this central theme in sociobiology namely altruism as applicable to resource management is by no means to negate the forces of aggression which co-exist with altruism. However, there is no doubt that the more altruistic humans becomes, greater are our chances for survival as a race, and better are the prospects for collective welfare and happiness through wiser, equitable and much more sustainable resource management.

IMPACTS OF PATENTING ON BIODIVERSITY-RICH DEVELOPING COUNTRIES

The impact of the stringent Intellectual Property Rights (IPR) system being championed by the Organization for Economic Cooperative and Development (OECD) countries, especially the USA, on the protection and sustainable use of the biodiversity in the underdeveloped countries, is yet to be sufficiently understood and is proving to be quite complex and worrisome.

This short paper is an attempt to summarise the current situation with respect to IPR and biodiversity, with a view to inform Jamaica's negotiations on this subject.

Current Popular Outlook

The rush to install and implant IPR biotechnological regulations by the rich countries has been seen as grossly self-serving and inimical to the interest of the poor countries. Two major reasons for this are biopiracy and the perceived immorality in patenting life.

(*a*) *Biopiracy*

A large portion of the world's genetic resources, including crop varieties, has resulted from innovation and conservation undertaken in the tropical and subtropical underdeveloped countries over long periods of time. Consequently, the knowledge and use of the biodiversity of these countries reside mainly with farmers, indigenous peoples and other local denizens. However, large companies from the developed countries are now poised to claim exclusive rights to produce and sell-modified forms of these materials, through the instigation of the present IPR system. This has triggered widespread protest by farmers and indigenous communities, who complain that the granting of patents to big companies on biological materials, such as plants, animals and human genes, will afford them large profits, for using the knowledge which have been generated, developed and used by locals in the underdeveloped countries for food, medicines, fibers, fuels, feeds and cultural functions over many decades and centuries. The transnational corporations involved stand to generate large revenues, while the local communities remain unrewarded, and in fact, face the threat in the future, of having to buy products from these companies, which were derived from these material, at high prices. The knowledge, innovation and husbandry efforts of these communities are not being sufficiently acknowledged when the legal IPR systems grant patents on genetic and biological materials, as well as, on living organisms. The tendency is to say that what is natural is in the public domain, but what arises in a laboratory is proprietary. The firms are collecting a range of living biodiversity materials, including soil microorganisms, animal and human genes, from the underdeveloped world and are fashioning new products containing the genetic materials of the collected biologicals, which they rush to patent to prevent competition. This is in stark contrast to the free sharing of biodiversity information by locals, who are the owners of the original material. These companies can reap, and are reaping large profits, from being able to raise prices for products, or by charging royalties from other firms wishing to use their technology. The genes of living organisms are the basic raw material of the new biotechnologies. Since the temperate countries have uniformly abused their environment and have reduced their biodiversity for their development, the tropics, where many of the underdeveloped countries are to be found, have an overwhelmingly wider range of variations and endemic species than would be expected. The underdeveloped world has therefore a decided comparative advantage in the currency of the future. This is only one of the few areas where the underdeveloped countries have a decided advantage and there appears to be a dedicated push to reduce this by unreasonable international maneuvering. If this is the case, all the shouts about helping the poor countries to develop, ring hollow and present a potential threat to world harmony and peace. The next century is already being termed the age of biology, as products derived from biological materials are expected to increasingly replace those made from metals and inorganic chemicals. Clearly then, those countries which have a strong agricultural base have a fair chance of propelling their economics forward and raising the standard of living of their peoples. The race by the big companies, under the protection of the IPR systems, to unethically exploit these materials from the poorer countries, has been dubbed, with some justification, bio-piracy. No small wonder then that there are an increasing number of legal challenges by civic, religious, indigenous and scientific groups, for the revocation of patents, for a wide variety of biologicals, derived from the biodiversity of these underdeveloped countries.

(*b*) *Patenting of life forms*

As these challenges proceed, a number of diverse groups including farmers, indigenous peoples, parliamentarians, religious leaders and Non-government Organizations (NGOs), are actively opposing the patenting of all life forms, or living things, by rich concerns in the indus-

trial states. The patenting of seeds and plants, as well as, the genes of indigenous peoples, are being vigorously opposed on all continents. For example, the Indian Parliament have recently voted to defer indefinitely a patent amendment bill to bring the Indian Patent Act in line with the World Trade Organization (WTO) treaty on IPR. The bill would have allowed the patenting of life forms. While the European Parliament has voted against the directive on "the legal protection of biotechnological inventions", which would have allowed for the patenting of biological materials and microbiological processes, with only few restrictions. Suffice it to say that, the patenting of certain biological processes may not stand up in court because they are insufficiently understood and is not more innovative they claiming to own a star because you are the first to pronounce that you have seen it.

Relevant International Conventions

There are two major international conventions which will have an immediate impact on the biodiversity status of poor countries. These are the trade-related intellectual property rights TRIPS agreement, and the Biodiversity Convention.

Although the WTO's Trade Related Intellectual Property Rights (TRIPS) agreement is very forthright about the compulsory patenting of microorganisms, plants and animals can be excluded, but protection of one kind or another is required for plant varieties. This clause however is up for review in four years.

The biodiversity convention recognizes farmers rights to their knowledge over the use of various techniques and also recognizes IPR's but at the same time uphold the need to aim for development, however, without detracting from the sustainable use of biodiversity.

Relevant regulations have been incorporated to check up the WTO from serving over to the large company's side, and not showing interest in poor countries intellectual property rights and the protection of biodiversity.

Scientific thoughts are linked to the value of biological diversity as a source of natural genetic resource holds valuable information and potential for claiming intellectual property rights will therefore play a crucial role in the national and international conventions concerning biodiversity, especially in the area of agriculture with reference to knowledge and practices of local communities and indigenous crop varieties where incentives affecting conservation and sustainable use of biodiversity. However, applications of IPR have been projected to be beneficial to biotechnology in a number of ways.

IMPACT OF GM CROPS AND GM FOODS

Checking the source of any food is one among the primary duties of individual consumers. Suppose I buy food not only for my young children, or aged parents, I want to know that it doesn't affect their health: If I believe providing that my belief is so strong that there is a chance, even if only a small one, that a food modified on using the genes of any fashion or British beef—is dangerous to their health, then I surely avoid to purchase that food unless the probability of the danger is exceptionally negligible or purely pressing reasons for why I should buy that food? This line of argument would mean that it is the duty of parents under their care not to buy GM food for their consumption.

It is also presumed that the few GM foods permitted to be sold in the EU are at least sold as value added foods, an individual therefore support, for example, the decision by a number of supporting higher authorities in England not to purchase GM foods for school meals. Therefore, you should buy GM food only for yourself and a mentally competent person after genuinely

discussing whether you ought to buy GM foods. One should buy welfare-friendly food.

However, genetic modification does make available a whole range of interesting possibilities that were unthinkable a few years ago and so the technology must be given a chance to reveal any benefits that it may have. The use of labeling has always been an important issue for consumers and we as a nation have slowly been following the lead of our U.S. counterparts in the task of labeling the nutritional content of our packaged foods. However, when it comes to the labeling of genetically-modified foods, food producers have been showing apprehension towards the use of this type of labeling. GM ingredients are already present in the food we consume today but for how long they have been there, no one is sure. In the recent years, there has been a public outcry to label these products but yet to no avail. In order to simplify the labeling issue, the current policies on labeling as well as both sides of the debate will be presented.

Currently, the policies of GM labeling have arisen from the collaboration of two government agencies, Health Canada and the Canadian Food Inspection Agency (CFIA). Health Canada set out to deal with the health and safety factors of the use of GM technology when preparing the guidelines whereas the CFIA is responsible for the non-health or safety issues to better inform the consumer and prevent misrepresentation or fraud. Together, the guideline that was proposed was **"the mandatory labeling of any foodstuff which poses a health or safety concern (*i.e.,* allergens, nutrient or compositional change).** Basically, that guideline doesn't account for everything else that is "safe" and is on the market, which leaves the consumer in the dark. Canada has not developed any stricter policies to deal with the remainder of the GM foods.

Canada is also a member of the Codex Alimentarius Committee on Food labeling (CCFL) which deals with the international issues of food labeling. So far, the CCFL proposed a similar policy on mandatory labeling as Canada's. The various countries worldwide are divided between those who want mandatory labeling on everything and others who don't. Countries that want complete mandatory labeling are Australia and India, meanwhile the U.S. and Canada seem satisfied with their current stance on labeling.

EU's Approach on Labeling

The safety of GM foods in European Commission are controlled by Regulation EC No. 258/97, which had introduced a mandatory premarket safety assessment for all novel foods produced after May 1997.

There are only four genetically-modified foods approved in the UK at present:

(*i*) **Soyabeans:** to be resistant to the herbicide glyphospate —> soya-based products and ingredients *e.g.,* soya flour and soya protein.

(*ii*) **Maize (corn):** to be herbicide resistant or to be poisonous to certain pests —> *e.g.,* starches and syrups.

(*iii*) **Tomatoes:** to be denser and drier, therefore better for puree production.

(*iv*) **Vegetarian rennet:** the genetic information for the chymosin enzyme in calf rennet has been copied into yeast cells —> can also be used to make cheese.

Health and safety, they labelled to enable consumer choice. C.I. says that surveys from many countries indicate widespread public support for foods, 92% of respondents of respondents to survey by the UK Consumers' Association wanted GM food to be labeled, regardless of the presence of a GM ingredient in the final produce (Nature "GM foods debate needs a recipe for restoring trust", 22 April, 1999).

Genetically-modified foods are inherently allergenic and/or harmful. By labeling, consumer have knowledge about the potential allergens and other health risks of the GM food (UCT "The genetically modified foods debate in South Africa ", 22 May, 1999).

The Government is determined that all food which contain genetically-modified material should be clearly labeled. Food will also require labeling, if there are any health or ethical concerns or if it contains a labeling of ingredients derived from GM soya and maize. Committee on the Ethics of Genetic Modification and Food Use recommended that a GM food should be labeled if it contains a gene derived from a human, or from an animal which is the subject of religious dietary restrictions; or if is plant or microbial material containing a gene derived from an animal. These recommendations are now a legal requirement, having been implemented under the Novel Foods Regulation 1997.

Cons

Labeling requires the availability of a technique that can guarantee the detection of transgenic DNA and protein, however, the detection of transgenic DNA or protein is not an easy task, and currently there is no officially validated protocol available for use. Currently, a few private companies and public laboratories are offering a PCR-based method for the detection of traces of specific transgenic genes in soya and maize. It would also be necessary to establish threshold levels above which labeling should be mandatory.

The Guidelines for Labelling of Genetically-Modified Foods

Pre-packed food must state in the list of ingredients for any soya or maize, which has been genetically-modified *e.g.,* "produced from genetically-modified soya" or "produced from genetically modified maize" or, those words may display in footnote to the list of ingredients related by means of an asterisk (*) to the ingredient concerned *e.g.,* soya * flour.

*genetically-modified.

Some approaches proposed by the European Commission that leads to the following labelling:

1. Voluntary labelling (*e.g.*, "this does not contain GMO…)" for certified non-GMO produce.

2. Mandatory labelling (*e.g.,* "this contains GMO…") for produce known to be of GMO origin or "this may contain…" in cases where material of GMO origin cannot be excluded but where no evidence of such material is available).

In order to make an educated decision on the matter, one needs to see the both sides of the issue.

Disadvantages

(*a*) Difficult to trace every use of GM technology. Unless you follow the farmer step by step, it is difficult to assess what has been modified, especially when the ingredients come from various farms.

(*b*) On what level should labeling be done?

i.e., do you label beef as being GM if the grass the cow ate was sprayed with GM pesticides?

(*c*) Not economical for farmers to segregate their GM crops from conventional ones.

(*d*) Would cause trade barriers between countries.

i.e., if Canada wanted to export foodstuffs to a country that had strict mandatory labelling on all GM foods, the receiving country may not accept the products if they have not been labeled appropriately.

Advantages

(*a*) Consumer knowledge of potential health concerns. *i.e.,* allergens.

(*b*) Increased customer awareness. *i.e.,* give them the choice of what to buy and eat such as for religious reasons or vegetarianism, etc.

(*c*) Economical for retailers to make two-tiered system of products : conventional and non-conventional.

Can charge higher prices for conventional foods if there is a demand for it.

Social and Political Issues

Food is of particular interest when considering biotechnology. Because we take it into our bodies, we have a fundamental right to know what it is, how it was processed and that it is safe. About 60 percent of our processed foods are genetically engineered. Therefore, it is important to concern about the pros and the cons sides of labeling genetically-modified foods.

Pros

European Union states that labeling must be applied to novel foods and their ingredients produced by means of genetic engineering when there is no substantial equivalence between a novel food and its original counterpart; when materials present in the novel food are not present in an equivalent non-modified product and may have consequences for the health of certain groups of people; when the novel food contains biotechnologically-derived material that may present ethical problems; and when living Genetically-Modified Organisms (GMOs) are present in the novel food (Nature biotechnology 16(10), 889, 1998 Oct).

In an Environics poll conducted in August 1999, 80 percent of respondents said they wanted labeling which told them what foods were Genetically Modified. Government and industry have responded with a voluntary labeling plan. That has some consumers dissatisfied. "I don't want to take the risk I would like to have them labeled, so that I can decide what I'm going to buy and not going to buy", "You hear about plants being altered with animal genetic material and *vice versa*. I don't know how that works but I'm really apprehensive about it". Therefore, consumer have the right to choose whether they want to buy GM food or not (Marketplace "Labeling Genetically Modified Foods" Dec. 7, 1999).

Lawsuit also argues that the Food and Drug Administration (FDA) should be treating genetic modifications as new food additives, which need to be tested for safety and approved before being sold. Moreover, the lawsuit claims that the agency should be treating all genetic modifications as additives (Nature "Lawsuit demands labels for modified foods", June 4, 1998).

Consumers International (CI) says that labeling is not just an issue of health and safety, they are labeled to enable consumer choice. CI says that surveys from many countries indicate widespread public support for comprehensive labeling of GM foods, 92% of respondents to survey by the UK Consumers' Association wanted GM food to be labeled, regardless of the presence of a GM ingredient in the final produce (Nature "GM foods debate needs a recipe for restoring trust", 22 April, 1999).

Genetically-Modified Foods are inherently allergenic and/or harmful. By labeling, consumers have knowledge about the potential allergens and other health risks of the GM food. (UCT "The Genetically-Modified Foods debate in South Africa" 22 May, 1999).

The Government is determined that all food which contain Genetically-Modified material should be clearly labeled. Food will also require labeling if there are any health or ethical concerns or if it contains a labeling of ingredients derived from GM soya and maize. Committee on

the Ethics of Genetic Modification and Food Use recommended that a GM food should be labeled if it contains a gene derived from a human, or from an animal which is the subject of religious dietary restrictions; or if is plant or microbial material containing a gene derived from an animal. These recommendations are now a legal requirement, having been implemented under the Novel Foods Regulation 1997.

Cons

Labeling requires the availability of a technique that can guarantee the detection of transgenic DNA and protein, however, the detection of transgenic DNA or protein is not an easy task, and currently there is no officially validated protocol available for use. Currently, a few private companies and public laboratories are offering a PCR-based method for the detection of traces of specific transgenic genes in soya and maize. It would also be necessary to establish threshold levels above which labeling should be mandatory.

Unit 3: Human Genome Project

ABSTRACT

Progress in molecular biology has enabled us to better understand human genetic disease, and has helped enhance the quality of life. This has been possible with technical developments to detect genetic disease presymptomatically. Presymptomatic testing would not yield information about the carrier status of an individual but also about other family members. Such information may lead to unreasonable beliefs and could alter social relationships. Ability to gain genetic information of the fetus has reduced the burden of suffering on human beings. Since fetal abortion is a sensitive issue, approach to such an information should be evaluated critically; and cautiously. Increase in genetic knowledge and capacity to manipulate life-form for convenience has raised several ethical questions and has challenged our moralistic and traditional responses. In India, little emphasis has been laid on ethical issues regarding genetic testing of disease. With adoption of new technology, it is high time that necessary steps are taken in this direction.

INTRODUCTION

Bioethics is a broad term and a very broad field of study. Bioethics can be defined as that discipline dealing with ethical issues raised by new developments in medicine and biological science. In the past (about 50 years ago), bioethics was used to solve simple ethical problems using Hippocrates postulates and Christian humanism. With advances in technology and cultural revolution, the traditional approaches of bioethics fail to account for certain complex events. Bioethics, as a separate formal field of study is roughly around 25 years old and one origin is the 1962 publication of *Life* magazine. Modern approaches to bioethics are derived from disciplines like philosophy, theology, medicine and law. The four cardinal principles that underline bioethics are confidentiality, beneficence, justice and autonomy. Medicine and other benefits of science have reached many social, cultural and religiously-diverse groups and acceptance of these benefits have triggered wide variety of responses, and has generated good public interest. In such a scenario, bioethics accounts for changes in both understanding and meaning. Application of bioethics involves three players: Physicians to practice beneficence, society to defend justice and patients to be granted autonomy. Many professionals need to be involved to accomplish these goals. A universal bioethical law is the need of the day. We wish to discuss three issues involving bioethics: presymptomatic genetic testing, prenatal diagnosis, and genetic manipulation.

Pre-Symptomatic Genetic Testing

Genetic testing for hereditary susceptibility to disease is new and the possibility of early diagnosis has changed the advent of genetic testing. Presymptomatic molecular diagnosis is important in identifying carriers in populations, which could enable us to stop manifestation of

disease prior to its occurrence. Molecular diagnostic tests are available for several diseases, such as Huntington's disease, cystic fibrosis and sickle-cell anemia. This has been dubbed as genetic prophecy. The information gained by molecular testing could be also misused. Ethical difficulties due to molecular presymptomatic testing arise at three different levels, in society, in employment and in insurance.

1. *Social Issues*

Genetic testing may lead to discrimination and stigmatization. In India, religions have strong hold over us and diseases are considered as punishment to evil deeds committed in the past or previous birth. Marriage is an important institution in our society. Mates are drawn from endogamous populations belonging to the same caste and religion. Individuals affected or carriers would be looked upon by our social system.

At an individual level acceptance to predisposition to a disease is a slow and painful process. The psychodynamics involved are rather complex. Another important aspect is the issue whether children should be aware of a disease they are going to suffer from, and particularly one which has no cure. Example of cystic fibrosis would throw more light on this issue. The simplest CF tests can pick 75% of the carriers. The accuracy of the diagnostic test is important. One-fourth of the carrier couples would be missed by this test. This leaves 56% of the carrier couples at risk. If both partners would be identified as negative by this test. Genetic screening opens new avenues for carriers and many of these may not be generally accepted by individuals or couples. These include: remain childless, by remaining single or voluntarily foregoing the opportunity to have children; Selection of a partner, who is not a carrier; To use assisted reproduction techniques in order to avoid having affected children. Each of the above options have raised controversies and are topics under intense consideration in the West. Acceptance of these would involve personal sensitivities.

Molecular testing can reveal information about relatives of an affected individual, who otherwise may not wish to know about their genetic status of the disease because this may lead to excommunication and discrimination of healthy individuals.

2. *Employment*

Denial of employment on the basis of information gained by genetic testing, is cause of serious ethical concern. The example of an American firm, which screened black employees for the presence of sickle-cell anemia is very apt here. Interest of an employer lies in investing into the expansion of business rather than on equipment for the safety of a specific employee. The better option for the employer is sacking the employee, citing reasons other than genuine. Re-employment might not be possible with a new employer for the same reasons.

3. *Insurance*

Insurance companies have started to think in a direction where a person predisposed to a particular disease may not be able to have insurance cover. The insurer could go for a test without the knowledge of the customer and basing on the results of the test insurance policy could be sold or withdrawn.

Prenatal Diagnostics

Prenatal diagnosis is the identification of disease of the fetus. The three main purposes of prenatal diagnosis are: to inform and prepare parents for the birth of an affected infant if any; to allow in utero treatment for postnatal treatment, if required; to indicate termination of an affected fetus. As of today, termination of affected fetus dominates over its management.

Technology today is capable of detecting a disease/disorders of the fetus to which it is, going to be susceptible in the future, from the mother's blood stream. We can well list out many diseases the unborn child is likely to be born with. Information gained from a battery of tests may affect the child in admission to school and college, employment and social standing. Steps to be taken towards proper use of prenatal diagnosis must be taken after careful and deliberate consideration. The fetus and abortion are sensitive issues. Ethical discussion on these topics is exhaustive. Much scholarship has been devoted here and in the west. It has become a major political argument.

(*a*) Human hazard: How safe are those involved in manipulating genomes? The evaluation or risk involved in working with vectors, proper disposal of laboratory by-products and critical evaluation of the manipulated organism is needed.

(*b*) Ecological hazard: Modified organisms can be sources of instability in an ecosystem. The disturbance may be observed after certain damage or it may go unnoticed. For example, recombinant DNA technology has enabled the production of insulin from *E.coli* strains. These organisms have been grown in large quantities and from them insulin harvested. Insulin is carefully regulated in the human body, and this equilibrium could be upset in an event, such as if insulin-producing bacteria could gain entry into human intestines, this would well mean a man-made problem. The second aspect is ecological hazards of monitored organism, which can be sources of instability in an ecosystem at various levels. Some effects may be beyond human observation. Involvement of intelligentsia is not only required, but the participation of the common man is very much necessary. A consensus should be reached based on ethical questions like, How far are we to proceed and develop genetic engineering? Do we want to assume basic responsibility for life on this planet? Should we take the evolution into our hands, which otherwise is a slow process in natural time scale?

Gene therapy is an effective way to correct gene deficiencies by replacing defective gene or supplementing it. Gene therapy is distinct and differs from other medical therapies, because it brings about changes in make up of an individual. Biblical saying goes 'God made man in his own image'. How far is man justified 'playing God', tampering with human genes. Gene therapy seems to be less mired with ethical problems than gene diagnosis. It was first performed in 1990 on adenosine deaminase (ADA) gene in the USA. In India, so far a gene therapy trial has not been reported. There are many unresolved issues to currently available gene therapies such as safety and stability of the vectors, behaviour of the gene after transfection, etc.

Basic considerations concerning gene therapy in India would be (*a*) to study the validity of the available protocols from abroad and evaluate as to how well they suit Indian conditions. (*b*) Indigenous development of techniques so as to reach the benefit to millions.

CONCLUSION

These issues of bioethics seem to have little relevance in India. Being a developing country, unemployment, hunger and poverty hold priority. However, bioethical issues should not be ignored. Genetic diseases in India have not drawn much attention and the geneticist is confined to the four walls of the laboratory, unaware of the prevailing situations. On one end of the spectrum it is the liberal, affluent and the educated class whereas on the other illiterate and poor. Of course, there is a sizable middle class too. Taking decisions can affect each of these groups in different ways. Risk and benefits have to be weighed keeping in view all these groups. The study of responses to topics, like prenatal diagnosis and genetics testing, can gather up to provide us with much information.

ETHICAL ISSUES OF THE HUMAN GENOME PROJECT

Introduction

Science is a human endeavour, so it is never perfect. Human beings today, perhaps as never before in history, find themselves perplexed in an enigmatic environment created as a result of human intelligence and activity. It took more than a decade since the start of the dedicated Human Genome Project, but the announcement of the draft full DNA sequence on 26 June, 2000 will be a historical day. Some people said, it will be remembered as the day when we learnt "what it means to be a human".

The initial proposal for the "Human Genome Project" is considered to be the 1986 editorial by Renato Dulbecco, in which he suggested that the fundamental problems related to cancer can be addressed by determining the sequence of the entire genome. Since then efforts have been continued at a global level to study the entire genome of human and a number of other model organisms. Already the complete genome of over 20 organisms was sequenced before scientists achieved the full draft human sequence. The molecular dissection of the genomes from so many species has unquestionably changed the scope for scientific and medical research.

However, as humankind applauds itself on the arrival of the "working draft" of the human genome, it is also a time to go back and explore what "human" means beyond times and scientific research. We need to reexamine how far human beings have come in an attempt to find our niche in nature and the ethical challenges that lie ahead in our attempt to redefine the meaning of life. From the very beginning, the Genome Project has been in the limelight for various reasons including the potential benefits and risks of this pioneer effort that will effect all parameters of life on this planet.

In this paper, I can only introduce some of the ethical issues, under the headings below:

1. *Medical Prospects*

The central thrust to the Human Genome Project was undoubtedly for biomedical research. The sequencing of the entire genome has already had a profound impact on the wider spectrum of clinical research, as it opens a new horizons for not only treatment of diseases but looking at the most fundamental causes of diseases. Already the genes for many diseases including for example, various cancers, Alzheimer's disease, and polycystic kidney disease, have been identified. Genomic sequencing allows rapid and accurate diagnosis for individuals. Initially the sequencing of human genome has led to a shift towards preventive medicine rather than curative, because further research is needed to develop therapies.

Earlier detection of genetic predispositions to disease can be used for late onset of genetically-inherited diseases. Such discoveries will enable us to work out which combinations of genes and environmental factors will lead to disease. In addition gene therapy is being tested. Other advantages of the sequencing include genetic testing and screening, and its use in reproductive technologies for preimplantation diagnosis.

Knowing the genes helps in understanding the molecular basis of medicine, so that we can make rational drug design, so that drugs can be designed to target the cause of the disease. The drugs can be designed for specific individuals, pharmacogenics, "custom drugs", which will change the prescription of drugs.

Also in the risk assessment of health damage and risks caused by radiation exposure, including low-dose exposure, and assessment of health damage and risks caused by exposure to mutagenic chemicals and cancer causing toxins, to reduce the likelihood of heritable mutations.

2. *Scientific Prospects*

One of the ideals of science is freedom for self-understanding. The influence of Human Genome Project on human self-understanding has been heralded as revolutionary. The sequencing of the genome will provide new clues on how we evolved. It would help us to understand what it means to be a human from different historical perspectives of bioarchealogy, anthropology, evolution, and human migration. Broader questions on the evolution of *Homo Sapiens,* the extent of human diversity, how much we share with nature or what makes us different from others will be answered by comparisons of genomes.

3. *Agricultural Prospects*

The parallel study of the genome of other organisms including those of plant and animal origin is progressing breeding in plant agriculture and livestock breeding. The rice genome has been completed. The sequencing of potato genome is underway. Pathogens have also been sequenced.

Genetically-Modified Organisms (GMOs) are already a hot topic in agriculture and livestock breeding. GMOs are organisms with genes modified for one or the other trait. We now have plants that are insect resistant, disease resistant, drought and cold resistant. We have farm animals that are healthier, more productive and disease resistant. Other plants and animals that are genetically modified include ones that incorporate vaccines in an edible form, or deliver hormones.

Genetic modification is also hotly debated. The eulogists, or proscience people, argue that the increase in the crop productivity with genetically-modified plants can be considered an option to the question of food security, given the number of hungry and chronically malnourished people in the world. The statistics show that we have over 800 million people who face starvation and malnourishment. It is our ethical duty to alleviate hunger and ensure access to food for all, given the number of lives lost and the loss in the quality of life. The technology behind genetic engineering is appealing and provides vision for many possibilities.

The people against it are sometimes called as anti-science people. There are many arguments against genetic modification, including “playing God”, safety, environment impact, potential loss of biodiversity, cost-effectiveness, access to the technology.

4. *Environmental Applications*

Taking into account the potential advantages of the Human Genome Project, similar public and private-funded projects were started to sequence the genomes of various microbes. Besides their role in disease, a further reason is that microbes play a critical role in biogeochemical cycles and they have been found surviving and thriving in amazing diversity of habitats often where no other life forms could exist. Annotation and analysis of microbial genomes will help in identifying and harnessing their capabilities to address the environmental problems, their use in energy production that can be used as biofuels, as an answer to the limited natural resources available. The challenges of environmental remediation, toxic waste reduction, environmental monitoring to detect the pollutants have been debated.

Despite our reliance on the inhabitants of the microbial world, we know very little about their nature and characteristics. Estimates show that microbes make up 60% of the Earth’s biomass and yet less than 1% of the microbial species have been identified. We cannot be reminiscent, nevertheless we have seen spectacular technologies like nuclear power creating a havoc in the past. There always lies the “fear of unknown”, and especially with so much of the microbial diversity uncharted there is a need for a cautious and critical approach.

5. ***Use in Forensic Science***

Forensic science is one of the fields that is also expected to be benefited from the genome sequencing, especially in the identification of criminals and victims of some tragedy. The genome project is expected to provide clues to examine the context and the environment in which the science and the law meet. The other examples of DNA uses for forensic identification include, identifying endangered and protected species, help in establishing relationships with family members. Though genome sequencing envisages a broader scope for forensic science, there are some sceptics about its effectiveness when used.

6. ***Economic Implications***

The Human Genome Project is the largest single biological project ever undertaken. For example, just the government budget in the United States started with US $28 million in 1988, and was at US $361 million in 2000, approximately a twelve-fold increase in the funding. Other governments also spent much, and private investment at least was equal to this. Such a huge monetary investment in itself testifies to the foreseen benefits out of the sequencing. Nevertheless the cost-effectiveness of the project was under criticism especially in early years. The critiques are apprehensive about existing gaps in the genome.

The questions of patenting of DNA, and genes by governments and private companies, intellectual property rights and benefit-sharing, have been particularly debated, and can be seen in the public announcements of first draft human genome sequence in year 2000.

The above questions though very significant, represent only one aspect of the economic implications. Another impact of the Human Genome Project is for developing countries who may have different priorities for investment in science. Also, multinational companies especially pharmaceutical companies will seek markets for designer drugs at low cost. This could be regarded as a conflict of interest between the needs of the common people to the interest of the governments and the private sector, especially for the people of the developing countries.

7. ***Ethical Concerns***

Since the beginning of the Human Genome Project, many ethical questions were raised. Recognising that, the U.S. Department of Energy (DOE) and the National Institutes of Health (NIH) allocated 3–5% of their total expenditure on HGP for the Ethical, Legal, Social Implications (ELSI) arising out of the Genome Project. This represented the world's largest bioethics program. The European Commission only started funding the HGP when it had set up an ELSI program. Since then there have been contemporary efforts going on to answer some of the bioethical challenges of the Human Genome Project.

Bioethics can be called as love of life. It is the concept. Bioethics could be viewed in descriptive, prescriptive and interactive ways. Interactive bioethics is discussion and debate between people and groups within society. Different sectors of society have been involved in the HGP, from ordinary people, patients, scientists, industry, governments, legal system, regional and international organizations, and the United Nations.

(a) **Beneficence:** In contemporary ethics, the principle of beneficence signifies an obligation to benefit others or to seek their good and it has been the foundation of many codes. Recalling that, the motive of the HGP is also based on the principle of beneficence to all, be it medical patients, health professionals, public institutions or private companies. Beneficence is the impetus for further research into ways of improving health and agriculture, and for protecting the environment. Beneficence supports the concept of experimentation, if it is performed to lead to possible benefits.

(*b*) Do no harm: Do no harm is a broad term, but it is the basis for the principles of justice and confidentiality and philanthropy. The judgement in most of the legal systems in the world follow the basic principle of "do no harm". It is also seen when we address the questions of balancing between benefits and the risks in the use of technologies. Two main ethical arguments in the Human Genome Project revolve around the moral concept of justice and confidentiality that are discussed separately.

(*c*) Human rights: There are three philosophical schools of thoughts to define what it means to be human. The social school, the developmental school and the genetic or the scientific school. These approaches try to distinguish the human organism from human beings. Human organism is used in the genetic or the scientific sense and human being is used in what may be called its normative, ethical or moral sense. Article 1 of Universal Declaration of Human Rights endows all human beings with reason and conscience, and Article 6 gives all human beings recognition as a person. In simple terms, the human body can not be used as an experimental "organism" without consent. This is enshrined in codes governing medical experimentation, such as the Nuremberg Code and the Helsinki Declaration.

(*d*) Animal rights: Animal experimentation in biological and medical sciences has been practiced for several millennia. Ethical guidelines for research on non-human animals are based on the assertion that animals are sentient, have conscious experiences, and feel pain and suffering, especially the vertebrate animals. The defenders argue that medical breakthrough come from animal experimentation. Usually the benefits of discoveries to humans generally overweigh the suffering of animals. The statistics of the use of animals can be misleading because the degree of harm varies widely.

Nevertheless, we can not ignore the moral status of animals. The boundaries of the moral obligations are not limited to the members of our own species. Though humans are considered superior in many respects such as self-awareness, rational decision-making, ability to communicate and think, and others, animals cannot be regarded as means of achieving our goals. We do not perform experiments on a severely disabled human either mentally or physically as our means to understand the disease. Macer argues in *Bioethics is Love of Life*, that the ethical limits of animal use intrinsic ethical factors like pain, self-awareness, future planning, value of being alive and individual love of life. Also extrinsic factors including human necessity or desire, human sensitivity to animal suffering, fertility in humans, other animals disapproval and religious status of animals, are important.

(*e*) Authority: Many people raised doubts about who should be involved in the sequencing of the genome and who should do the work. The project required a multi-disciplinary approach involving medical experts, biologists, bioethicists, information specialists, computer experts and many others for data banking and analysis. The multidisciplinary authorisation of the Genome Project has on one hand rewarded it with speeding the process, on the other hand it aroused conflict between different groups because of the inherent interests of their respective fields.

(*f*) Autonomy: The concept of autonomy in bioethics gives each individual the recognition of the human capacity for self-determinism and being different in spite of sharing same DNA which is regarded as a "common heritage". This is also true in the choices we make. Personal choices are expressed in law as rights. With the advent of new technologies we have the ethical challenge of respecting people as equals, allowing them to exercise their personal values and decisions. Freedom of expression is parallel to autonomy, but it is debatable that it should not encroach the territory of others.

(*g*) Ownership: The competition for the genome sequencing between the publically funded Genome Project and the world's leading private company Celera Genomics is well known. The fear behind this is the unwarranted risk of data ownership. Since it is agreed that all human beings share the same genome, from the ethical perspective, the sequenced data should be owned by all human beings, as it is emphasized in UNESCO's Universal Declaration of Human Genome and Human Rights.

(*h*) Justice: The other side of the possibility for transforming medicine is who will actually benefit? Will everyone have access to such revolutionized health care? There is a fear that it might widen the gap between rich and poor. In the developing world, the Human Genome sequencing may not be the first choice for better treatment, where millions of people do not even have access to basic medical treatment. The poor tropical countries could be more interested in deciphering the genomes of disease causing bacteria, viruses or parasites that could provide new target of drugs vaccines or antibiotics. Even in rich countries, not all will benefit equally. It is agreed that it will be extremely difficult and in some cases impossible to provide best treatment to all in need, but a rational and balanced approach is needed so that the people in developing world have their share of benefits from these advancements.

(*i*) Confidentiality and privacy: It will not be surprising if in the next few years we all will be able to get our individual genomes sequenced. Already distinctive genetic information can be obtained from a simple test. Despite sharing a common genome each individual is distinct in both physical and behavioural characteristics which are determined to some extent by our genes. Those are very personal and confidential to all of us.

The privacy of the genetic information is reinforced not only because of the presumed prospects for the use of such information beyond medical reasons, for instance, discrimination of the "genetic underclass" at different levels, but also to retain the trust with people and respect for person's autonomy. However, there are exceptions considered by some if it will avoid physical harm to someone, for example.

(*j*) Responsibility: The responsibility of use or the misuse of the genetic information is an individual decision, but what is useful for one may not be useful for others. The definition of "misuse" is also debatable. So the responsibility of the misuse of genetic information cannot be put on the people involved in genetic research, though private companies may be exceptions depending on the use. If "genetic discrimination" occurs, it will be the fault of social values rather than of the technology.

(*k*) Scientists and social duty: Scientific freedom to research what scientists desire is included in the fundamental human rights under the UN Declaration of Human Rights, and in the UNESCO Charter. Researchers and scientists have a basic right to experimentation, scientific research and to explore new things. Scientific research and experimentation may not always give the positive, correct or accurate results. Many people regard the HGP as an extension from the desire to know ourselves. Inarguably there are benefits for public good already from the genome projects. But there always lies the danger of misusing scientific freedom. The scientific community has to bear the moral responsibility for using very powerful knowledge, as agreed in the UNESCO Declaration on the Human Genome and Human Rights.

(*l*) Consequences: The consequences of the HGP are affirmative only when used in a proper way, for the well being of all of humanity. The tremendous potential of the technology is unquestionable. It gives hope and choices for the future. It depends on the action and the motive behind the use of genetic sequencing and further use of the gained genetic information. We have to use the precautionary principle approach, which says we need to be very careful to avoid harm.

THE HUMAN GENOME DIVERSITY PROJECT

One of the expansions of the HGP, and population genetics, is to explore human diversity, under the Human Genome Diversity Project (HGDP). There are about 5000 ethnic groups in the world with diverse races, cultures, languages and even gene pools. Even to study some of these will help us understand human history. This proposed scientific contribution to world culture has been controversial due to various political, social and ethical reasons. The concept of ethnicity has been exploited in the arguments related to the diversity project, be in favour or against.

The study of genetic epidemiology and the provision of scientific data to population studies, should help us to resolve some anthropological and archaeological questions. These include to identify and help in preventing the loss of endangered populations, reasons for human migration and study of genetic diseases that are unique or prevalent to one population.

The Human Genome Organisation (HUGO) has proposed guidelines to address some of the ethical and legal requirements related to HGDP, which addressed the issues like informed consent, benefits to the sampled populations, confidentiality, intellectual property rights, public understanding and some others. However, these guidelines still failed to address many other issues like easy exploitation of the voluntary altruistic act of contributing the DNA, the danger of commercialization and misuse of genetic heritage by the heads or the local governments. There are also culturally-specific risks that could be identified as intra-community risks, risk to shared identity, risk to established social equilibria and risk to cultural and moral authority.

The ethical concerns are not limited to the above. Some of the ethnic populations are those who live in their own world, away from the scientific and technological world, follow their own cultural and religious beliefs. In that context, the prospects of the HGDP may be biased to the interests of scientific community, rather than upliftment of the targeted communities in their basic livelihood, or at the same time keeping respect for their racial, cultural and religious identities. There may be a long-term danger of eugenics which can not be ignored because eugenic measures often end up with racial or social group overtones, more than breeding from the “best genes”.

The Human Genome Diversity Project has been a catalyst for consideration of the ethical issues that arise during population genetics research, but itself has been plagued by the concerns to the point where the original plan is unlikely to be completed because technical strategies have evolved to help reduce the number of persons who need to be sampled originally the project called for sampling of several dozen representative persons from 500 population groups to assemble genetic linkage maps of each. However, as Resnik discusses, ethical concerns were raised by some representatives of some of these groups, and some other NGOs who had general concerns about genetic research, and over recent trends to patent human genes and cell lines isolated from particular persons.

I have entitled this paper ethical opportunities rather than problems because I think we have much to learn from the issues raised and the process. Some of the mechanisms developed to answer the concern, such as the notion of group consent, have potential to be used elsewhere. The attention paid to the HGDP has made population geneticists more cautious of the types of projects they conduct, and made the ethical review more concrete. We have seen the emergence of guidelines, including the Human Genome Organization (HUGO) Ethics Committee (1997), Statement of Principled Conduct of Genetic Research, which is being applied to genetics research in general. Ironically, probably the HGDP with the attention it pays to ethics review will have less ethical problems than most population genetics and anthropology research that

continues today, so these researchers still have more to learn from the debate over the HGDP.

Personally, the HGDP was also an ethical opportunity to learn of more diverse views over a scientific project. The need to support diversity is well recognized in international law, but not always in ethics or practice. My work in generating dialogue and revising drafts of a UNESCO International Bioethics Committee (IBC) subcommittee report on population genetics gave me the privilege to meet and contact sincere individuals on both sides of the debate. More clearly, the UNESCO report did not support the HGDP; rather it raised a number of ethical issues and gave a balanced view. Sadly, the opportunity for ethical dialogue at an international level by a mixed committee of all sides has been stalled since 1997 (Macer et al., 1998), and the issues are being addressed, or not, on regional level in a way which still has some critics.

Resnik (1999) has raised some of the major concerns and presents some discussion, and solutions to the problems, namely racism, gene patenting, exploitation, protecting indigenous cultures and people, informed consent and group consent. I will just discuss some of these and supplementary issues in terms of the opportunities presented.

Some of the other ethical issues of population genetics research addressed by the UNESCO report include: How to obtain free and informed consent from individuals and groups; Selection and participation; Use of the knowledge gained; Return of benefits to participants; Clash of world-views; Does the right not to know apply to communities? Who speaks for a community? Ownership of genes and derived knowledge; Public understanding and racism or eugenics; stigmatization and genetic reductionism; and International oversight of anthropologists and geneticists. The key points of the UNESCO report were:

(*i*) No endorsement of a particular population genetic project;

(*ii*) Call for establishment of a separate ethical committee that is available to all population genetics researchers;

(*iii*) Discussion of variety of ethical, ethnic and social issues.

Although there is scientific evidence to suggest that there will be little population genetic diversity found that is unique to one particular group, there is also a logical possibility that there may be distinct genetic features that make one genetic group distinct from others. The fact is that, while eugenics was founded on racism, eugenics today does not have to be linked with racism. Those who continue to link their eugenics with racism will not be dissuaded by scientific evidence, since racism is an attitude of mind, or prejudice.

Current population genetics research is under the oversight of different layers of control which vary widely around the world. This oversight ranges from the discretion of individual researchers, consent from the persons who provide the tissue samples, consent from the groups being studied, to several layers of ethical committee. International regulations on research involving human subjects are clear that informed consent is needed. Some funding agencies demand ethical review, such as NIH-funded research in the USA, and here the NRC Report discussed by Resnik has its biggest impact. Some universities in the world also demand ethical review, and the trend is to have more review.

The HGDP makes us consider our roots and their importance (or not) in modern society. There are a few thousand population groups in the world, only some members of these are active as indigenous people. “How many generations link you to your home?” is related to the definition of who is indigenous ? Maybe all people are indigenous to somewhere; however, minority groups have reason to be more afraid of abuses than those of a majority. The alleged abuses of genetics that they raise are relevant to us all, as they raise questions of how the knowledge will be used as well as how the research will be conducted?

Some of the ethical issues related to human genetics in general, such as the use of genetic data in prenatal diagnosis (Macer, 1998). Some data may be useful for developing genetic tests, and an important issue is commercialization and use of the results of the collected DNA and cells. Financial returns are not the only form of benefits of research results, which could be returned to subjects of research. The feedback of results to the communities concerned should also help to foster a greater sense of community identity in the face of aggressive cultural imperialism by industrial superpowers. But perhaps the most poignant problems of many populations involved in population genetics research is in the realm of public health. The provision of health and medical care, however, should be appropriate to the cultural and social context of the community and should be sustained.

At the community level, the health data could be utilized as an ethical opportunity for the improvement of local community health. Thus, benefits should also flow back to the groups and communities in the form of contributing to the formulation and implementation of local and national health care policies that would enable communities to better their positions. Commercial benefits could be expressed in other ways. While there could also be provision for a one-time gift of cells or blood with no conditions, as is found in some tissue donation forms for blood and body tissues, can one individual sign away commercial rewards to future research knowledge for the population to which they belong? It may be technically possible to conduct the new HGDP, as population genetics research among students of an international university, with them giving their cells to science, and whether their group like it or not, the students represent their population.

The application of the ethical principle of informed consent and respect for integrity is a complex process at the level of populations. In order to ensure that the potential subjects understand the goals of research, the risks involved, the use to which research results could be put, and the rights of the groups and individuals under study, careful consideration is needed. If group consent is accepted, it is then a task to identify the most appropriate persons with whom to communicate, the persons from whom clearance should be obtained, and the appropriate content and media of communication. Research will need to take account of the group's social organization, goals and aspirations, cultural values, and laws (both statutory and customary).

Various groups of indigenous peoples have expressed their irritation with past population genetics research, which they claim has been conducted without prior consultation and in a way where consent was obtained in terms inconsistent with their cultural norms. In this respect the HGDP presents an opportunity for dialogue and ethical research, even if a population decides not to be a part of the research, this will be an accomplishment in bioethics in itself. The Mataatua Declaration on Cultural and Intellectual Property Rights of Indigenous Peoples of June 1993 (5) called for a halt to the HGDP until its impact has been discussed. Article 3.5 of the Declaration calls "for an immediate halt to the ongoing 'Human Genome Diversity Project' (HUGO) until its moral, ethical, socio-economic, physical and political implications have been thoroughly discussed, understood and approved by indigenous peoples". The Declaration is actually not anti-science, and includes a call for involvement in scientific research, recommendation 2.11, "Ensure current scientific environmental research is strengthened by increasing the knowledge of indigenous communities and to customary environmental knowledge".

If this opportunity is taken for researchers to be subject to greater scrutiny, the same holds true for the media whose duty of honest, scientific reporting and preservation of privacy needs to be underscored. Whole populations, communities and the researchers themselves have often been wrongly depicted and wrongly represented with the resulting unjust labeling and discrimination. Such practices only serve to undermine public confidence and participation in research. Let us hope that all will be responsible.

THE NEED FOR A STRATEGIC FRAMEWORK

The Universal Declaration on Human Rights in 1948, has given ethical parameters an objective mode to justice and the decision-making. They are regarded as fundamental rights to all human beings and invigilate a wide spectrum of basic human requirements.

There were various public and professional regulatory policies formulated since the beginning of the HGP, seeing its wide implications. The HGP did not arise from the consensus by all scientists or doctors that information was badly needed, rather it was initiated within the U.S. Department of Energy. So, the project owes its existence to the government that advocated the project, even though human genetics would have eventually reached the same goal. A major objection to the policies, was who should formulate the policies? It is for society to decide how much of its wealth is devoted to scientific research. Once the decision is made there should be justifiable medical and scientific reasons for allocating the funds. There might be nothing wrong with the concept, or the technology is judged adequate, but still there remains the question as to whether or not it is reasonable to divert the allocation of resource from other activities to mega sequencing of the genome.

The present policies reflect the criteria to tackle the immediate or the short term effects, for example, for medical uses or discrimination. They are more individual person oriented. But there is still a need for policies that could prelude the consequences of the genome sequencing in the long term.

The majority of the policies primarily are focussed or shadowed by the legal systems in the individual countries which are dominant players in the project. The need for international approaches (including education and guidelines) is based on several arguments: shared biological heritage and destiny of human beings in all "nations"; the transitory nature of "nations" and the precedents for international law to protect the common interest of humanity; the common perceptions and the bioethical reasoning of peoples around the world — universal bioethics. There is a need for a universal strategic framework, given the globalisation and overlapping interests of government, social and business sectors, although we may also say that some of the misunderstandings and doubtful presumptions crop up because the overarching principles, rights and duties defined by our laws, can sometimes be too much. The need is for a framework that is representative of the interests of all the concerned people directly or indirectly involved, a framework that is based on the principles of ethics and moral boundaries that value respect for humanity as their foremost principle.

FOETAL SEX DETERMINATION

Genetic amniocentesis is a special procedure that can be performed at 15-16 weeks to obtain a sample of amniotic fluid that is sent to a genetics lab for **chromosome analysis** and **alpha-fetoprotein (AFP).** The most common indication for this test is **advanced maternal age** (age 35 or older at the estimated date of delivery). The amniocentesis is performed under ultrasound guidance using sterile technique. Clinical studies have shown that there is less than a 0.5% risk of miscarriage related to this procedure.

Chorionic villus sampling (CVS) at 10-11 weeks. CVS is a special procedure in which a tiny sample of placental tissue is removed and sent to a genetics lab for chromosome analysis. The CVS is done with ultrasound guidance using sterile technique. The advantage of CVS is that it can lead to an earlier diagnosis than amniocentesis. We can obtain results within 24 hours. Clinical studies have shown that there is a 0.8% risk of miscarriage related to this procedure.

At 18–20 weeks, a detailed **ultrasound** survey of the fetal anatomy can help determine the presence or absence of certain problems with the fetus. Some genetic disorders can be identified with certain ultrasound signs. Our OB/GYN physicians are **experts at OB/GYN ultrasound,** which is very important, since the quality and accuracy of the ultrasound is greatly dependent on both the quality of the equipment and the skill of the person doing the ultrasound. While ultrasound is very useful in making a diagnosis, no ultrasound exam can be considered 100% accurate.

THE INDIAN LAW ON ABORTION

Section 312 of the Indian Penal Code, defines the offence of 'causing miscarriage' as follows "whoever voluntarily causes a woman with child to miscarry shall, if such miscarriage be not caused in good faith for the purpose of saving the life of the woman, be punished with imprisonment of either description for a term which may extend to 3 years, or with fine, or with both; and, if the woman be quick with child, shall be punished with imprisonment of either description for a term which may extend to 7 years, and shall also be liable to fine".

Medical Termination of Pregnancy Act, 1971 (MTP) Act) was implemented from April, 1972. Implemented rules and regulations were again revised in 1975 to eliminate time consuming procedures for the approval of the place and to make services more readily available. The MTP Act, 1971 preamble states "an Act to provide for the termination of certain pregnancies by registered medical practitioners and for matters connected therewith or incidental thereto".

SOCIAL IMPLICATIONS OF THE ACT

Govt. of India has enacted much social legislation since independence. In practice we find that these very good social legislation have remained in the books and the govt. is not able to implement these laws. Take for example, the antidowry bill or the Child marriage bill or the antisati bill. Child marriages still takes place. The MTPA is the only social legislation that has found wide acceptance without any resentment. Unwanted pregnancy is a social stress in all societies. Before the MTP Act, unwanted pregnancy was managed by resorting to illegal abortion, infanticide or deserting the newborn in lonely places. Now with the MTP Act, the social fears are considerably reduced and the urban and the rural community have taken advantage of the Act. Patters of sexual and reproductive behaviour have changed significantly over the years. Most important change is the increase in the premarital sex in all societies. There is also an increase in the out of wedlock births. There is increasing freedom enjoyed by the teenagers in social life. This often results in increased teenage pregnancy. The tragedy is that physiologically and anatomically there is a trend towards earlier maturation while process of social development is lagging behind. Young boys and girls are exposed to knowledge and information, and values not shared by parents or older members of the family.

The impact of the MTP Act should be judged in the context of changing social values and attitudes. The social implications of MTP in unmarried girls and MTP in married woman are different. MTP in married woman is not considered as a social stigma, whereas MTP in unmarried girls is not easily accepted and hence girls are taken to other distant places for MTP, and hence the girl's social future is not destroyed. This social legislation has certainly reduced incidence of suicide in these women because they can seek safe abortion under the law. The health of the woman has also shown improvement because of the MTP facilities. The acceptance of the family planning methods after MTP has also increased. It is paradoxical that though the community is taking the advantage of MTP services, they want to maintain secrecy and not let the neighbour know about it.

Here negative aspects of the MTP Act have also to be considered. Though the MTP services are now available in rural areas, we are not sure of its effectiveness and safety. The high-risk cases are not recognized and MTP is performed in such cases without adequate back-up services. This results in immediate complications and long-term morbidity in term of infertility, menstrual disturbances and pelvic inflammatory disease (PID). These long-term complications may have social implications in the form of broken marriages, divorce, and promiscuity. Mehlar, Director General of WHO has said, "because of serious effects of legalized abortion on the health and reproductive capacity of woman, upon the stability of family and upon the morality of country specially its youth, it should be carried out only in a hospital and that to by a gyne-cologist".

How true are the words in context of the present situation in India? The Govt. must see that MTP is done by trained surgeons only and that too in a hospital set-up. Gynecologist must also share some blame for MTP complications. The young girls and women come to the gynecologist at any time for MTP. This is because they do not want to inform the parents or other family members about it. Some deaths on operation table have been reported because of the practice of performing quick MTP without proper checkup. It is necessary that gynecologists do not perform MTP at unearthly hours and without proper facilities to fight complications if they do arise. The Indian MTP Act is most liberal in practice, it almost amount to "abortion on demand".

It is said that termination of pregnancy is performed on flimsy ground such as 'approaching examination', 'Marriage in the family', 'going on a tour or vacations', etc. It is said that medical fraternity encourages such unnecessary terminations more often for financial reasons. It is necessary to check this trend of pregnancy termination on flimsy grounds. It is often not realized that frequent and unnecessary pregnancy termination can result in infertility and PID. Though the MTP Act was never thought to be used as a method of family planning it is unfortunately used as an alternative to regular methods of family planning by many women. It is the social responsibility of obstetricians to counsel all patients coming for MTP about the use of some contraception. It should be emphasized that contraception use is much safer than MTP. The use of emergency contraception (EC) by women should be encouraged in time of contraceptive accidents or failures. At present easily available methods for emergency contraception is oral contraceptive, and intrauterine device. The Obstetrician must remember that some woman coming for MTP may be HIV positive if they are used to multiple partners or their husbands/partner is used to multiple sex partners. There is a risk of STD/HIV transmitted to medical and paramedical staff if precautions are not taken. It is debatable whether HIV testing should precede all MTP procedures. The Govt. of India has banned prenatal sex determination test for selective female feticide and violation of law is punishable with fine and imprisonment. The centers for prenatal test facilities have to be certified by govt. agencies. These laws are enacted to reduce selective female feticide which is a good objective, it is not clear if these laws have reduced MTP procedures for selective female feticide. These social legislations succeed provided there will be an active participation of the community and the medical people. The social purpose of these laws will not be served unless the medical people and the community co-operate in its implementation.

ETHICAL ISSUES IN MTP

Though many people believe that MTP is immoral but in today's social context it is a reality. The ethical and legal issues regarding MTP currently revolve around the quality of service, right of the dependent minor to give her own consent for MTP, fetal viability and the coercion. A few of the ethical issues are highlighted here.

Unsafe Abortion

It is estimated that 40-60 million abortions take place throughout the world and half of them are performed by unauthorized persons, mostly in developing countries, with grave consequences (WHO, 1990). Health education and community awareness are the basic aspects of its prevention.

Illegal abortions are performed much more frequently in India with their disastrous results even today in spite of liberalization of the Medical Termination of Pregnancy Act. Two cases of unsafe abortions are reported where the procedure was carried out by doctors without any training in midwifery and family planning. One patient had extensive small bowel injury secondary to uterine perforation but survived whereas the other expired due to septicaemia, peritonitis, disseminated intravascular coagulopathy following uterine perforation.

Induced abortion signifies voluntary or willful termination of pregnancy, whether permitted by law or not, before viability. Induced abortion may be illegal (mostly septic abortions) or legalized abortions usually Medical Termination of Pregnancy (MTP). Unfortunately the decline in illegal abortions that one might have expected when abortions were legalized has not taken place.

The term "unsafe abortion" proposed by the World Health Organization (WHO) lately has been accepted by most other international health institutions. Unsafe abortion means "abortion not provided through approved facilities and/or person". Unsafe abortion is one of the great neglected problems of health care in developing countries .

Duration of Pregnancy and MTP

1st trimester abortion is more ethical because it is simpler, and kinder and safer than 2nd trimester abortion. In 2nd trimester mother may feel the fetal movement and in this stage MTP, often she suffers from physiological trauma and sense of guilt.

MTP in Teenage

Combinations of various factors, like sexual fantasies, attraction to the opposite sex, lack of sex education and also media influence the young people for teenage sex, premarital sex, much more than in the past. Proper counseling, sex education and adolescent health care are must.

Prenatal Diagnosis and MTP

Ethical controversies always appear in prenatal screening and specific termination. A great dilemma exist in couples for making decision for termination of handicapping abnormalities. Things become worse where the pregnancy is much wanted one. It may be accepted by many couple, but may not be by some for religious and moral reasons. In less severe chromosomal defects as with sex chromosomal aneuploidies, it is agonizing decision for the couples. So, proper counseling must be done and every view of the couple must be respected.

Sex Selective Abortion

Sex selective abortion is of grave social concern. It is unethical and illegal too. Social and family pressures are such that in spite of legislation pregnant woman does opt for prenatal sex determination for selective female feticide. We must realize that selective feticide challenges equality of sex and status of women. Failure to recognize equality of sex is the sign of ageing and decaying society.

Young girls are conspicuous by their absence in Fatehgarh Sahib, a small town in the prosperous state of Punjab. On the streets, in homes, in schools and even in meetings to discuss the abhorrent practice of pre-natal sex determination, mothers are accompanied only by little boys. Not surprising, since Fatehgarh district has the dubious distinction of having the lowest child sex ratio in the country. With the child sex ratio (0–6 years) plummeting from 874 girls for every 1000 boys in 1991 to an abysmal 754 in 2001, it is apparent that something is seriously amiss.

ETHICAL ISSUES LEADING TO LEGAL ISSUES

Legal problem may arise in the following issues:

- Termination done without proper counseling and consent.
- Continuation of pregnancy following MTP. It is an ethical problem where pregnancy is continued in spite of attempted termination both in respect of mother and fetus. If the baby in later life comes to know that he/she was an unwanted one a serious psychological set back leading to hatred to the parent might be imparted upon. From legal point of view, it may be stamped as act of negligence.
- Among many reasons of failed MTP, 'faulty techniques' is one.
- Improper diagnosis and MTP. It is unethical to attempt MTP without confirming the pregnancy. Often ectopic pregnancy is missed. This might endanger the woman's life and consequently invite litigation.
- Morbidity and even mortality following the procedure attributable to negligence and improper care given to her in follow-up.
- MTP in Primigravide is of grave ethical concern. The first pregnancy is the most welcome one to a family, so the physical and mental trauma imparted to her cannot be replaced. Moreover there is a chance of infection leading to morbidity and even in future, secondary infertility – a cure to womanhood in our society.

GENETIC STUDIES ON ETHNIC RACES

When the sequencing of the human genome was completed in 2000, it was heralded as evidence that race was a cultural construction with little base in science. The sequencing apparently shows that approximately 99.9% of the human genome is the same in everybody, and that there is greater genetic variation within each race than there is between races.

According to Dr. Craig Venter of Celera Genomics, one of the organizations involved in the sequencing, the level of genetic similarity shows that : "Race is a social concept, not a scientific one". There is only one race, Dr. Venter and other scientists at the National Institutes of Health have unanimously declared: the human race.

Dr. Harold Freemen of the North General Hospital in Manhattan told the New York Times that only about 0.01% of our genes are responsible for our external appearance, on which we base our racial categorizations. The humans brain is finely attuned to recognize differences in appearance to facilitate differentiating between individuals. We, therefore, place great emphasis on appearance. But these differences in appearance translate into only tiny differences in our genetic make-up.

Many scientists and academics believe that this new information challenges the legitimacy of racial categorizations and shows that race is a meaningless notion. In 1997, the American Anthropological Association, which has published an official statement on race, urged the government to cease using racial categories.

Other writers, such as Professor Joseph Graves, author of "The Emperor's New Clothes: Biological theories of race at the Millennium", have questioned the value of racial categories in medicine. However, not everyone agrees with this statement. Some researchers continue to see racial classifications as scientifically useful, while others, such as surgeon general Dr. David Satcher, believe that the evidence correlating race with health disparities in America warrants the continued use of the categories.

(a) Genetic Science and American-Indian Identity

The American-Indian identity is a complex matter. As with many contemporary ethnic identities, genetics, in the form of ancestry and blood quantum, plays an important role in identity construction. While many American-Indian tribes require that potential members show a particular blood quantum before they are accorded tribal membership, few tribes currently use genetic tests to determine eligibility.

However, genetic tests to identify ancestry are becoming available. A new Texas-based company, Family Tree DNA Genealogy by Genetics, Ltd. performs genetic testing for Native American ancestry on individual customers. The company carries out mitochondrial DNA testing to determine Native American ancestry inherited through a direct line of maternal descent. They can also perform Y chromosome testing on men. These tests are, of course, limited to exclusively the maternal or paternal line.

There are no reports of American-Indian tribes requiring or relying on DNA testing for membership, but the Western Mohegan an officially unrecognised tribe of the upper Hudson, has reportedly tested the DNA of its members in an effort to prove they possess American-Indian blood.

In February 2000, a piece of legislation was introduced into the Vermont Legislature that proposed that the State's Commissioner of Health establish standards and procedures for DNA-HLA testing to determine the identity of an individual as a Native American. It was intended that the results of such testing would be conclusive proof of the Native American ancestry. The bill failed to become law before the end of the 1999 legislative session and has not been reintroduced. However, during its short life it provoked a strong reaction. Debra Harry, the director of the Indigenous Peoples Council on Biocolonialism called it "outrageous" and said that it "demonstrates a complete lack of knowledge about genetic". One internet site even set up a petition against the bill.

But Kimberly Tallbear, of the International Institute for Indigenous Resource Management, has suggested that critics misinterpreted the Vermont bill, which she says was intended to provide an additional, rather than sole, means of establishing Indian heritage. Nevertheless, she notes that the bill is an example of an approach that assumes "that a person's culture and identity are chiefly biologically determined rather than being socially constructed". She also cautions that "scientists, policy makers, and others who advocate that genetic testing be used to determine culture or identity, imply a eugenics type belief that genetic markers are synonymous with culture and somehow guarantee cultural continuity".

Genetic testing is approached with a certain amount of skepticism and resistance by some in American-Indian circles. Tallbear considers this reluctance to be in part based on "an increasingly widespread belief among Indian people that to entertain ideas about the benefits of science and technology is to be anti-traditional". She also believes that tribes fear that scientific establishments cannot be trusted with their genetic resources. This concern to retain control over genetic material is evidenced in The Mataatua Declaration on Cultural and Intellectual Property Rights of Indigenous Peoples signed at the 1993 First International Conference on

Cultural and Intellectual Property Rights of Indigenous Peoples and in the 1995, Declaration of Indigenous Peoples of the Western Hemisphere Regarding the Human Genome Diversity Project.

(*b*) *The Caste System in India*

Are caste-based hierarchies of racism? This question was the topic of a heated dispute between the Indian government and representatives of the **Dalit** (or "Untouchables") at the 2001 World Conference on Racism in Durban, South Africa. The Dalit argued that caste-based discrimination is a type of racism and that their political struggles should be included in the agenda of the conference. The Indian government resisted this argument, arguing that the caste system is unconnected to race.

The Indian government eventually succeeded in almost wholly excluding any substantive discussion of caste at the conference. However, a recent genetic study suggests that higher caste groups in India are genetically more similar to Europeans and that lower castes are more similar to Asians. Some observers have taken this study as evidence that discrimination based on caste is more similar to discrimination based on race than defenders of the caste system admit.

The caste system in India is a hierarchical social structure divided into four levels called **varnas.** Each varna is an endogamous group that has traditionally been assigned differing social roles. From highest to lowest, those occupying the four varnas are:

1. Brahmins

2. Kshatriyas

3. Vaishyas

4. Shudras

However, beyond the four varnas there is a fifth group called **Achut,** or Untouchable. Members of this last group are considered too polluted even to be included in the caste hierarchy. They are outcasts, and they are assigned roles that, though necessary, are thought too low for members of the four varnas.

In recent times, Gandhi tried to give the untouchables a less offensive name, while still preserving the category. He called them Harijan, or children of Hari, a Hindu deity. Going even further, the constitution of the modern, democratic state of India outlawed the practice of untouchability in an attempt to efface the concept. Yet, despite this effort, the concept of untouchability is still part of the caste system as it survives in India today.

In reaction to this concept and the oppression it has been used to justify, the untouchables of India have organized themselves into a political group demanding equal rights under the democratic constitution of India. As a start, they have discarded the terms "Untouchable" and "Harijan' and have adopted the title, "Dalit", which means broken, torn asunder, or crushed. Further, they have attempted to make the world aware of their situation. The Dalit community argued that their case needed to be heard at the World Conference on Racism in Durban, but the Indian government vigorously opposed this argument. They argued that the Dalits are not a racial group and thus have no place in a conference on racism.

The debate between the Dalits and the Indian government raises complex questions about the nature of race and caste. These questions have been complicated still further by a recent study suggesting that the notion of caste originated in the concept of race. A study led by Michael Bamshad of the University of Utah indicated that higher castes in India have more European genetic markers while the lower castes including Dalits have more Asian genetic markers. Critics of the caste system have taken this study as a refutation of the argument that caste was originally based not on birth but on the "nature" of individuals.

(*c*) *The Cohanim*

According to Jewish tradition male descendants of Moses' brother Aaron were selected by God to serve as priests. These priests are known as the Cohanim.

Given that the Y chromosome is passed from father to son one might expect that male members of the Cohanim living today would carry similar Y chromosomes. In addition, it might be expected that these Y chromosomes would show that the Cohanim and the Levites (the Jewish caste of which Moses was a member) shared a common ancestor in the Temple period, approximately 3,000 or 2,000 years ago.

A study conducted by researchers from the United Kingdom and Israel showed that although the Y chromosomes of Levite men are very diverse, Cohen Y chromosomes are relatively homogenous. In a sample of 306 Jewish males from Israel, Canada and the United Kingdom the researchers found that a particular series of polymorphisms, known as a *haplotype*, was noticeably common among both Ashkenazic and Sephardic Cohanim. This haplotype is called the *Cohen model haplotype* or CMH. Identification of the CMH in a high proportion of men belonging to a particular group can be used to support claims that the group has Jewish ancestry. From the results of their study the researchers were also able to estimate how long ago the Cohanim they sampled had shared a common ancestor. They estimated that the common ancestor had lived approximately 2,600 years ago, sometime between the Exodus and the destruction of the first temple.

(*d*) *The Lemba*

The Lemba are a black Southern African Bantu speaking group who claim to have Jewish ancestry. They observe customs that suggest a Jewish link such as not eating pork, male circumcision, and keeping one day a week holy. According to their oral history, they came to Africa from "Sena in the north by boat". The original group, which is said to have been almost entirely male, made its way to the coasts of Eastern Africa. If the Lemba do indeed have Jewish ancestry then one might expect to find a similarity between the Y chromosomes of Lemba men and those of Jewish men living in other parts of the world.

In a recent study, the Y chromosomes of around 136 Lemba were compared to the Y chromosomes of Ashkenazic and Sephardic Jews, Yemeni and non-Lemba Bantu speakers. The study's results were suggestive of a genetic history the Lemba that is not incompatible with the Lemba's oral tradition. Researchers found evidence of Semitic origin in the Lemba, although it was not clear whether this origin was Jewish or Arab, or a mixture of both.

The study also found that the Lemba carry the Cohen modal haplotype (CMH) at a frequency similar to that found in Jewish populations. The CMH has been suggested as a signature for the ancient Hebrew population. In fact, the Lemba men who showed a very high frequency of the CMH were those who identified themselves as belonging to the **Buba** clan. The Buba is recognized as the senior of the twelve Lemba clans, being the oldest and for some ritual purposes the most important. In many ways the Buba may be likened to the Cohen. Non-Lemba Bantu speakers in the study did not carry the CMH.

The researchers concluded that the Lemba most likely have a mixture of Jewish, Arab and Bantu origins, although the CMH present in Lemba men could have an exclusively Jewish origin. The genetic evidence is therefore consistent with the Lemba oral tradition of a Jewish origin.

(*e*) *The Black Seminoles*

The Seminoles are an American Indian tribe that originated in Florida around the beginning of the 18th century. Over a period of approximately 200 years slaves in neighbouring

states fled to Florida, where many found refuge among the Seminole Indians. These former slaves fought alongside the Seminoles in a number of wars against the Americans and were relocated to Oklahoma in the mid 1800s, where the tribe was given a reservation. In 1866, the Seminoles in Oklahoma signed a treaty with the United States government under which the blood Seminoles and the Black Seminoles were accorded equal rights. Thereafter, the Black Seminoles of Oklahoma were known as "Freedmen".

In July 2000 the Seminole Nation of Oklahoma passed a resolution to amend their tribal membership criteria to require possession of one-eighth Seminole Indian blood. This new focus on blood quantum is not only in breach of the 1866 treaty, but it also has the effect of expelling many of the Freedmen from the tribe because many cannot show possession of Indian blood.

At a time when using genetics to prove identity is becoming more and more common, the Freedmen are an interesting case primarily because genetics has traditionally taken a back seat in the construction of their "Indianness". Their membership of an American-Indian tribe has for generations been based on a shared history, rather than on shared Indian genetics. However, the Freedmen's membership of the nation is now under threat as the tribe moves over to an identity system that places genetics above history, that values blood quantum over contribution to tribal affairs.

The story of the Freedmen offers a very unusual understanding of what it can mean to belong to an American Indian tribe. It also illustrates how genetics is becoming a popular way of defining identity.

Unit-4: Stem Cells Research

INTRODUCTION

Research on stem cells is advancing knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. This promising area of science is also leading scientists to investigate the possibility of cell-based therapies to treat disease, which is often referred to as **regenerative or reparative medicine.**

Stem cells are one of the most fascinating areas of biology today. But like many expanding fields of scientific inquiry, research on stem cells raises scientific questions as rapidly as it generates new discoveries.

The NIH developed this primer to help readers understand the answers to questions such as: What are stem cells? What different types of stem cells are there and where do they come from? What is the potential for new medical treatments using stem cells? What research is needed to make such treatments a reality?

Stem cells have two important characteristics that distinguish them from other types of cells. First, they are unspecialized cells that renew themselves for long periods through cell division. The second is that under physiologic or experimental conditions, they can be induced to become cells with special functions such as the beating cells of the heart muscle or the insulin-producing cells of the pancreas.

Scientists primarily work with two kinds of stem cells from animals and humans: **embryonic stem cells** and **adult stem cells,** which have different functions and characteristics that will be explained in this document. Scientists discovered ways to obtain or derive stem cells from early *mouse* embryos more than 20 years ago. Many years of detailed study of the biology of mouse stem cells led to the discovery, in 1998, of how to isolate stem cells from *human* embryos and grow the cells in the laboratory. These are called **human embryonic stem cells.** The embryos used in these studies were created for infertility purposes through ***in vitro*** **fertilization** procedures and when they were no longer needed for that purpose, they were donated for research with the informed consent of the donor.

Stem cells are important for living organisms for many reasons. In the 3-to-5-day-old embryo, called a **blastocyst,** stem cells in developing tissues give rise to the multiple specialized cell types that make up the heart, lung, skin, and other tissues. In some adult tissues, such as bone marrow, muscle, and brain, discrete populations of adult stem cells generate replacements for cells that are lost through normal wear and tear, injury, or disease.

It has been hypothesized by scientists that stem cells may, at some point in the future, become the basis for treating diseases such as Parkinson's disease, diabetes, and heart disease.

Scientists want to study stem cells in the laboratory so they can learn about their essential properties and what makes them different from specialized cell types. As scientists learn more about stem cells, it may become possible to use the cells not just in **cell-based therapies,** but also for screening new drugs and toxins and understanding birth defects.

However, as mentioned above, human embryonic stem cells have only been studied since 1998. Therefore, in order to develop such treatments scientists are intensively studying the fundamental properties of stem cells, which include:

(*i*) determining precisely how stem cells remain unspecialized and self renewing for many years; and

(*ii*) identifying the **signals** that cause stem cells to become specialized cells.

What are the unique properties of all stem cells?

Stem cells differ from other kinds of cells in the body. All stem cells—regardless of their source—have three general properties: they are capable of dividing and renewing themselves for long periods; they are unspecialized; and they can give rise to specialized cell types.

Scientists are trying to understand two fundamental properties of stem cells that relate to their **long-term self-renewal:**

(*i*) Why can **embryonic stem cells** proliferate for a year or more in the laboratory without differentiating, but most **adult stem cells** cannot; and

(*ii*) What are the factors in living organisms that normally regulate stem cell **proliferation** and self-renewal?

Discovering the answers to these questions may make it possible to understand how cell proliferation is regulated during normal embryonic development or during the abnormal **cell division** that leads to cancer. Importantly, such information would enable scientists to grow embryonic and adult stem cells more efficiently in the laboratory.

(*a*) *Stem cells are unspecialized:* One of the fundamental properties of a stem cell is that it does not have any tissue-specific structures that allow it to perform specialized functions. A stem cell cannot work with its neighbors to pump blood through the body (like a heart muscle cell); it cannot carry molecules of oxygen through the bloodstream (like a red blood cell); and it cannot fire electrochemical **signals** to other cells that allow the body to move or speak (like a nerve cell). However, unspecialized stem cells can give rise to specialized cells, including heart muscle cells, blood cells, or nerve cells.

(*b*) *Stem cells are capable of dividing and renewing themselves for long periods:* Unlike muscle cells, blood cells, or nerve cells—which do not normally replicate themselves—stem cells may replicate many times. When cells replicate themselves many times over it is called *proliferation*. A starting population of stem cells that proliferates for many months in the laboratory can yield millions of cells. If the resulting cells continue to be unspecialized, like the parent stem cells, the cells are said to be capable of long-term self-renewal.

The specific factors and conditions that allow stem cells to remain unspecialized are of great interest to scientists. It has taken scientists many years of trial and error to learn to grow stem cells in the laboratory without them spontaneously differentiating into specific cell types. For example, it took 20 years to learn how to grow **human embryonic stem cells** in the laboratory following the development of conditions for growing mouse stem cells. Therefore, an important area of research is understanding the signals in a mature organism that cause a stem cell population to proliferate and remain unspecialized until the cells are needed for repair of a specific tissue. Such information is critical for scientists to be able to grow large numbers of unspecialized stem cells in the laboratory for further experimentation.

(*c*) *Stem cells can give rise to specialized cells:* When unspecialized stem cells give rise to specialized cells, the process is called **differentiation.** Scientists are just beginning to understand the signals inside and outside cells that trigger stem cell differentiation. The inter-

nal signals are controlled by a cell's **genes,** which are interspersed across long strands of DNA, and carry coded instructions for all the structures and functions of a cell. The external signals for cell differentiation include chemicals secreted by other cells, physical contact with neighboring cells, and certain molecules in the **microenvironment.**

Therefore, many questions about stem cell differentiation remain. For example, are the internal and external signals for cell differentiation similar for all kinds of stem cells? Can specific sets of signals be identified that promote differentiation into specific cell types? Addressing these questions is critical because the answers may lead scientists to find new ways of controlling stem cell differentiation in the laboratory, thereby growing cells or tissues that can be used for specific purposes including **cell-based therapies.**

Adult stem cells typically generate the cell types of the tissue in which they reside. A blood-forming adult stem cell in the bone marrow, for example, normally gives rise to the many types of blood cells such as red blood cells, white blood cells and platelets. Until recently, it had been thought that a blood-forming cell in the bone marrow—which is called a **hematopoietic stem cell**—could not give rise to the cells of a very different tissues, such as nerve cells in the brain. However, a number of experiments over the last several years have raised the possibility that stem cells from one tissue may be able to give rise to cell types of a completely different tissue, a phenomenon known as **plasticity.** Examples of such plasticity; include blood cells becoming **neurons,** liver cells that can be made to produce insulin, and hematopoietic stem cells that can develop into heart muscle. Therefore, exploring the possibility of using adult stem cells for cell-based therapies has become a very active area of investigation by researchers.

What are embryonic stem cells ?

What stages of early embryonic development are important for generating embryonic stem cells?

Embryonic stem cells, as their name suggests, are derived from embryos. Specifically, embryonic stem cells are derived from embryos that develop from eggs that have been fertilized ***in vitro***—*in an* **in vitro fertilization** clinic—and then donated for research purposes with informed consent of the donors. They are *not* derived from eggs fertilized in a woman's body. The **embryos** from which **human embryonic stem cells** are derived are typically four or five days old and are a hollow microscopic ball of cells called the **blastocyst**. The blastocyst includes three structures: the **trophoblast,** which is the layer of cells that surrounds the blastocyst; the **blastocoel,** which is the hollow cavity inside the blastocyst; and the **inner cell mass,** which is a group of approximately 30 cells at one end of the blastocoel.

How are embryonic stem cells grown in the laboratory?

Growing cells in the laboratory is known as **cell culture**. Human embryonic stem cells are isolated by transferring the **inner cell mass** into a plastic laboratory culture dish that contains a nutrient broth known as **culture medium.** The cells divide and spread over the surface of the dish. The inner surface of the culture dish is typically coated with mouse embryonic skin cells that have been treated so they will not divide. This coating layer of cells is called a **feeder layer**. The reason for having the mouse cells in the bottom of the culture dish is to give the inner cell mass cells a sticky surface to which they can attach. Also, the feeder cells release nutrients into the culture medium. Recently, scientists have begun to devise ways of growing embryonic stem cells without the mouse feeder cells. This is a significant scientific advancement because of the risk that viruses or other macromolecules in the mouse cells may be transmitted to the human cells.

Over the course of several days, the cells of the inner cell mass proliferate and begin to

crowd the culture dish. When this occurs, they are removed gently and plated into several fresh culture dishes. The process of replating the cells is repeated many times and for many months, and is called **subculturing**. Each cycle of subculturing the cells is referred to as a **passage**. After six months or more, the original 30 cells of the inner cell mass yield millions of embryonic stem cells. Embryonic stem cells that have proliferated in cell culture for six or more months without differentiating, are **pluripotent,** and appear genetically normal are referred to as an **embryonic stem cell line.**

Once cell lines are established, or even before that stage, batches of them can be frozen and shipped to other laboratories for further culture and experimentation.

What laboratory tests are used to identify embryonic stem cells?

At various points during the process of generating embryonic stem cell lines, scientists test the cells to see whether they exhibit the fundamental properties that make them embryonic stem cells. This process is called *characterization*.

As yet, scientists who study human embryonic stem cells have not agreed on a standard battery of tests that measure the cells' fundamental properties. Also, scientists acknowledge that many of the tests they do use may not be good indicators of the cells' most important biological properties and functions. Nevertheless, laboratories that grow human embryonic stem cell lines use several kinds of tests. These tests include:

- growing and subculturing the stem cells for many months. This ensures that the cells are capable of long-term self-renewal. Scientists inspect the cultures through a microscope to see that the cells look healthy and remain **undifferentiated.**
- using specific techniques to determine the presence of **surface markers** that are found only on undifferentiated cells. Another important test is for the presence of a protein called Oct-4, which undifferentiated cells typically make. Oct-4 is a transcription factor, meaning that it helps turn **genes** on and off at the right time, which is an important part of the processes of cell **differentiation** and embryonic development.
- examining the chromosomes under a microscope. This is a method to assess whether the chromosomes are damaged or if the number of chromosomes has changed. It does not detect genetic mutations in the cells.
- determining whether the cells can be subcultured after freezing, thawing, and replating.
- testing whether the human embryonic stem cells are pluripotent by allowing the cells to differentiate spontaneously in cell culture; manipulating the cells so they will differentiate to form specific cell types; or injecting the cells into an immunosuppressed mouse to test for the formation of a benign tumor called a **teratoma.** Teratomas typically contain a mixture of many differentiated or partly differentiated cell types—an indication that the embryonic stem cells are capable of differentiating into multiple cell types.

As long as the embryonic stem cells in culture are grown under certain conditions, they can remain undifferentiated (unspecialized). But if cells are allowed to clump together to form **embryoid bodies,** they begin to differentiate spontaneously. They can form muscle cells, nerve cells, and many other cell types: Although spontaneous differentiation is a good indication that a culture of embryonic stem cells is healthy, it is not an efficient way to produce cultures of specific cell types.

So, to generate cultures of specific types of differentiated cells—heart muscle cells, blood cells, or nerve cells, for example—scientists try to control the differentiation of embryonic stem cells. They change the chemical composition of the culture medium, alter the surface of the culture dish, or modify the cells by inserting specific genes. Through years of experimentation

scientists have established some basic protocols or "recipes" for the **directed differentiation** of embryonic stem cells into some specific cell types (Fig. 4.1).

If scientists can reliably direct the differentiation of embryonic stem cells into specific cell types, they may be able to use the resulting, differentiated cells to treat certain diseases at some point in the future. Diseases that might be treated by transplanting cells generated from human embryonic stem cells include Parkinson's disease, diabetes, traumatic spinal cord injury, Purkinje cell degeneration, Duchenne's muscular dystrophy, heart disease, and vision and hearing loss.

How are embryonic stem cells stimulated to differentiate?

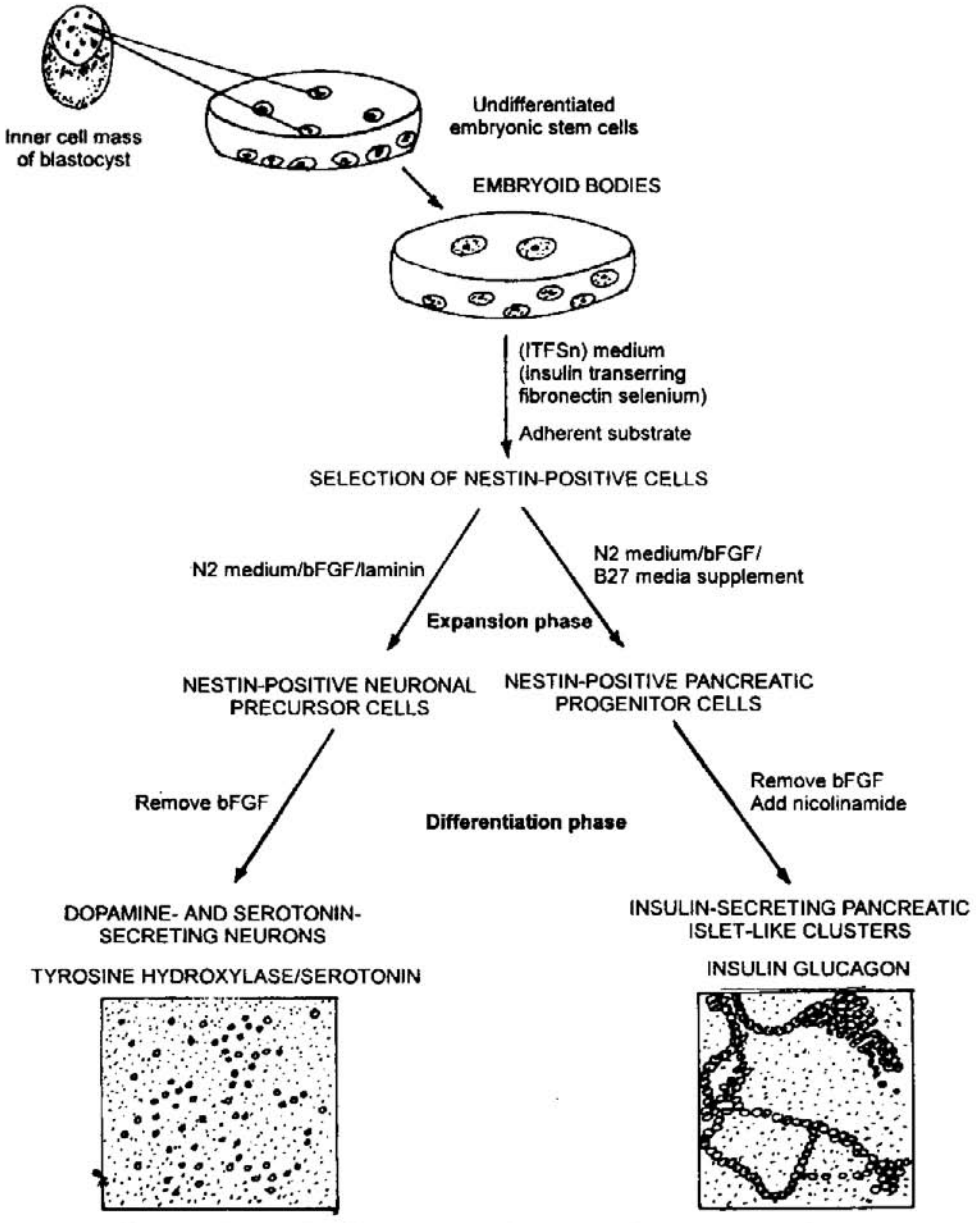


Fig. 4.1. Directed differentiation of mouse embryonic stem cells.

What are adult stem cells?

An adult stem cell is an **undifferentiated** cell found among differentiated cells in a tissue or organ, can renew itself, and can differentiate to yield the major specialized cell types of the tissue or organ. The primary roles of **adult stem cells** in a living organism are to maintain and repair the tissue in which they are found. Some scientists now use the term **somatic stem cell** instead of adult stem cell. Unlike **embryonic stem cells, which** are defined by their origin (the **inner cell mass** of the **blastocysts**), the origin of adult stem cells in mature tissues is unknown.

Research on adult stem cells has recently generated a great deal of excitement. Scientists have found adult stem cells in many more tissues than they once thought possible. This finding has led scientists to ask whether adult stem cells could be used for transplants. In fact, adult blood forming stem cells from bone marrow have been used in transplants for 30 years. Certain kinds of adult stem cells seem to have the ability to differentiate into a number of different cell types, given the right conditions. If this differentiation of adult stem cells can be controlled in the laboratory, these cells may become the basis of therapies for many serious common diseases.

The history of research on adult stem cells began about 40 years ago. In the 1960s, researchers discovered that the bone marrow contains at least two kinds of stem cells. One population, called **hematopoietic stem cells,** forms all the types of blood cells in the body. A second population, called **bone marrow stromal cells,** was discovered a few years later. **Stromal cells** are a mixed cell population that generates bone, cartilage, fat, and fibrous connective tissue.

Also in the 1960s, scientists who were studying rats discovered two regions of the brain that contained dividing cells, which become nerve cells. Despite these reports, most scientists believed that new nerve cells could not be generated in the adult brain. It was not until the 1990s that scientists agreed that the adult brain does contain stem cells that are able to generate the brain's three major cell types—**astrocytes** and **oligodendrocytes,** which are non-neuronal cells, and **neurons,** or nerve cells.

Where are adult stem cells found and what do they normally do?

Adult stem cells have been identified in many organs and tissues. One important point to understand about adult stem cells is that there are a very small number of stem cells in each tissue. Stem cells are thought to reside in a specific area of each tissue where they may remain quiescent (non-dividing) for many years until they are activated by disease or tissue injury. The adult tissues reported to contain stem cells include brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin and liver.

Scientists in many laboratories are trying to find ways to grow adult stem cells in **cell culture** and manipulate them to generate specific cell types so they can be used to treat injury or disease. Some examples of potential treatments include replacing the dopamine-producing cells in the brains of Parkinson's patients, developing insulin-producing cells for type I diabetes and repairing damaged heart muscle following a heart attack with cardiac muscle cells.

What tests are used for identifying adult stem cells?

Scientists do not agree on the criteria that should be used to identify and test adult stem cells. However, they often use one or more of the following three methods:

(*a*) Labelling the cells in a living tissue with molecular markers and then determining the specialized cell types they generate.

(*b*) Removing the cells from a living animal, labelling them in cell culture, and transplanting them back into another animal to determine whether the cells repopulate their tissue of origin and

(*c*) Isolating the cells, growing them in cell culture, and manipulating them, often by adding growth factors or introducing new **genes,** to determine what differentiated cells types they can become.

Also, a single adult stem cell should be able to generate a line of genetically-identical cells — known as a **clone**—which then gives rise to all the appropriate differentiated cell types of the tissue. Scientists tend to show either that a stem cell can give rise to a clone of cells in cell culture, or that a purified population of candidate stem cells can repopulate the tissue after transplant into an animal. Recently, by infecting adult stem cells with a virus that gives a unique identifier to each individual cell, scientists have been able to demonstrate that individual adult stem cell clones have the ability to repopulate injured tissues in a living animal.

What is known about adult stem cell differentiation?

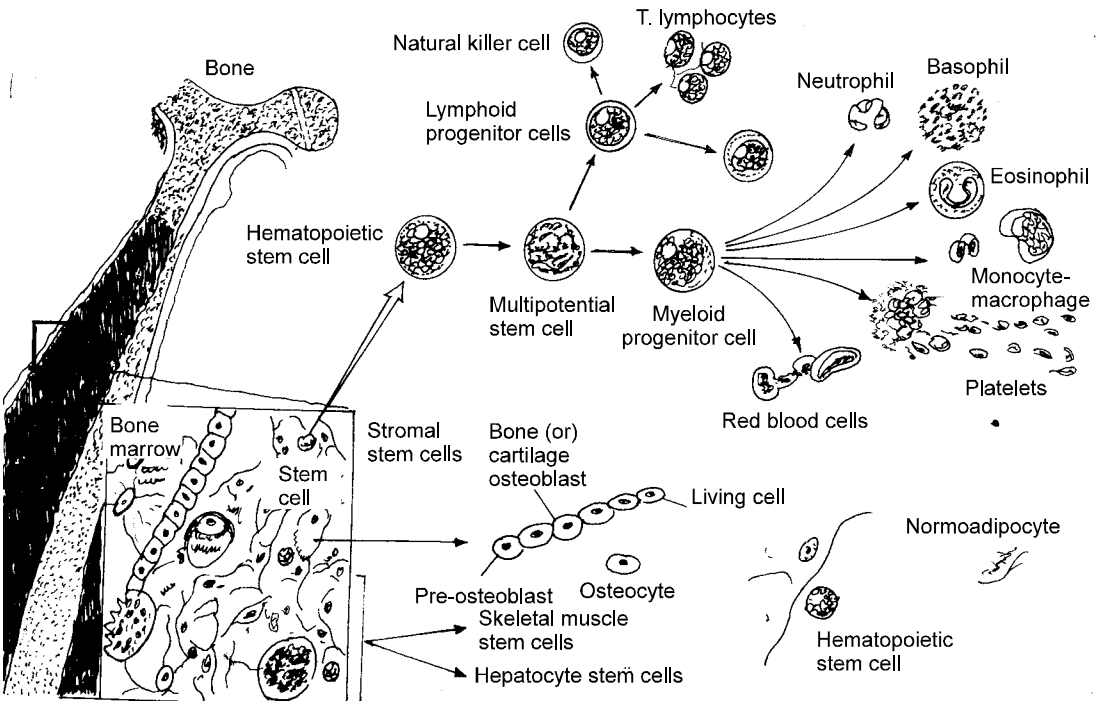


Fig. 4.2. Hematopoietic and stromal stem cell differentiation.

As indicated above, scientists have reported that adult stem cells occur in many tissues and that they enter normal **differentiation** pathways to form the specialized cell types of the tissue in which they reside. Adult stem cells may also exhibit the ability to form specialized cell types of other tissues, which is known as **transdifferentiation** or **plasticity.**

Normal differentiation pathways of adult stem cells. In a living animal, adult stem cells can divide for a long period and can give rise to mature cell types that have characteristic shapes and specialized structures and functions of a particular tissue. The following are examples of differentiation pathways of adult stem cells (Fig. 4.2).

Hematopoietic stem cells give rise to all the types of blood cells: red blood cells, B lymphocytes, T lymphocytes, natural killer cells, neutrophils, basophils, eosinophils, monocytes, macrophages, and platelets.

Bone marrow stromal cells **(mesenchymal stem cells)** give rise to a variety of cell types : bone cells (osteocytes), cartilage cells (chondrocytes), fat cells (adipocytes), and other kinds of connective tissue cells such as those in tendons.

Neural stem cells in the brain give rise to its three major cell types: nerve cells (neurons) and two categories of non-neuronal cells—astrocytes and oligodendrocytes.

Epithelial stem cells in the lining of the digestive tract occur in deep crypts and give rise to several cell types: absorptive cells, goblet cells, Paneth cells, and enteroendocrine cells.

Skin stem cells occur in the basal layer of the epidermis and at the base of hair follicles. The epidermal stem cells give rise to keratinocytes, which migrate to the surface of the skin and form a protective layer. The follicular stem cells can give rise to both the hair follicle and the epidermis.

Adult stem cell plasticity and transdifferentiation. A number of experiments have suggested that certain adult stem cell types are **pluripotent.** This ability to differentiate into multiple cell types is called *plasticity* or *transdifferentiation*. The following list offers examples of adult stem cell plasticity that have been reported during the past few years:

Hematopoietic stem cells may differentiate into: three major types of brain cells (neurons, oligodendrocytes, and astrocytes); skeletal muscle cells; cardiac muscle cells; and liver cells.

Bone marrow stromal cells may differentiate into: cardiac muscle cells and skeletal muscle cells.

Brain stem cells may differentiate into: blood cells and skeletal muscle cells.

Current research is aimed at determining the mechanisms that underlie adult stem cell plasticity. If such mechanisms can be identified and controlled, existing stem cells from a healthy tissue might be induced to repopulate and repair a diseased tissue (Fig. 4.3).

What are the key questions about adult stem cells?

Many important questions about adult stem cells remain to be answered. They include :

- How many kinds of adult stem cells exist, and in which tissues do they exist?
- What are the sources of adult stem cells in the body? Are they "leftover" embryonic stem cells, or do they arise in some other way? Why do they remain in an differentiated state when all the cells around them have differentiated?
- Do adult stem cells normally exhibit plasticity, or do they only transdifferentiate when scientists manipulate them experimentally? What are the **signals** that regulate the **proliferation** and differentiation of stem cells that demonstrate plasticity?
- Is it possible to manipulate adult stem cells to enhance their proliferation so that sufficient tissue for transplants can be produced?
- Does a single type of stem cell exist—possibly in the bone marrow or circulating in the blood—that can generate the cells of any organ or tissue?
- What are the factors that stimulate stem cells to relocate to sites of injury or damage ?

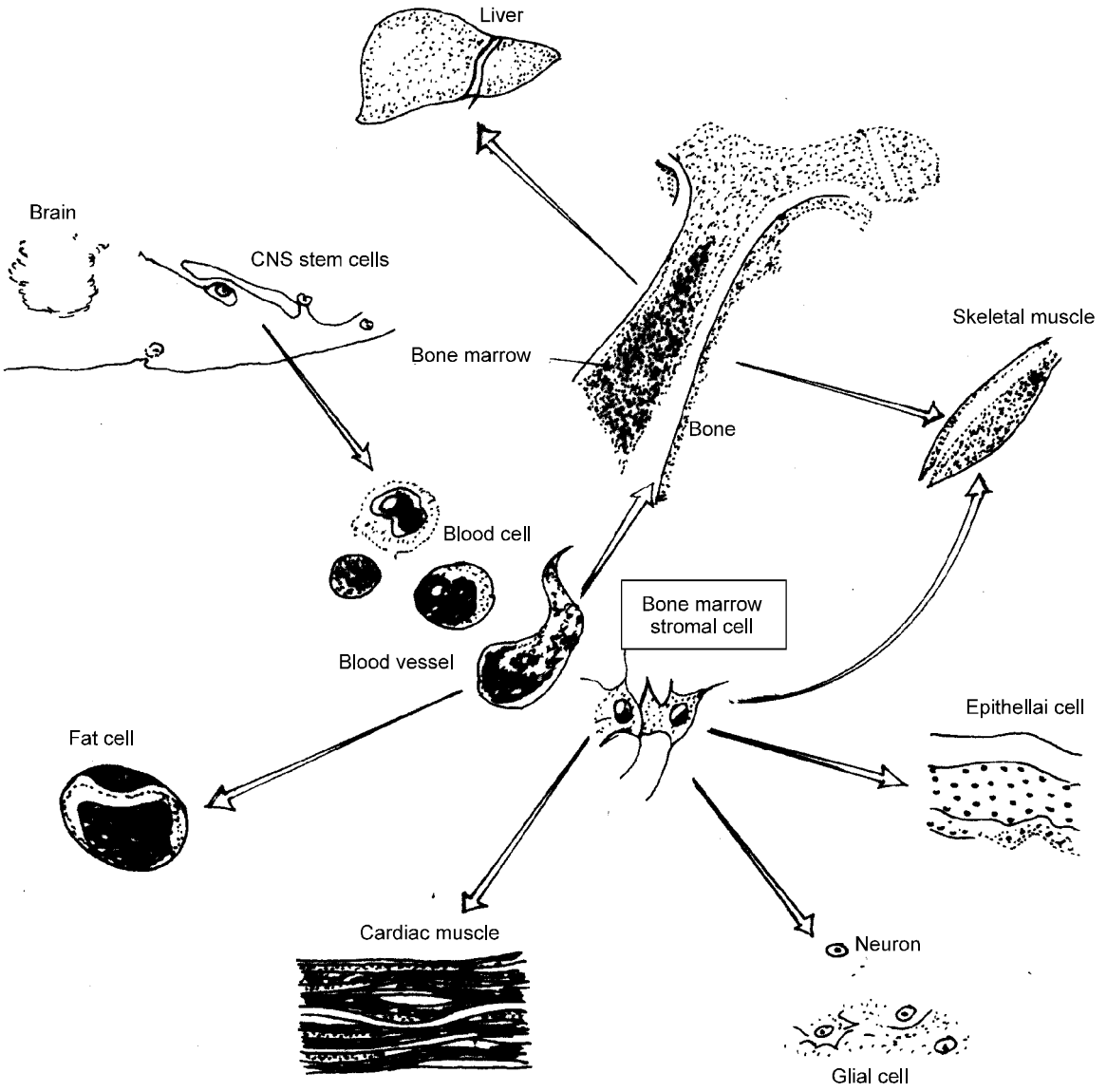


Fig. 4.3. Plasticity of adult stem cells.

APPLICATIONS OF STEM CELLS

There are many ways in which human stem cells can be used in basic research and in clinical research. However, there are many technical hurdles between the promise of stem cells and the realization of these uses, which will only be overcome by continued intensive stem cell research.

Studies of **human embryonic stem cells** may yield information about the complex events that occur during human development. A primary goal of this work is to identify how **undifferentiated** stem cells become differentiated. Scientists know that turning **genes** on and off is

central to this process. Some of the most serious medical conditions, such as cancer and birth defects, are due to abnormal **cell division** and **differentiation.** A better understanding of the genetic and molecular controls of these processes may yield information about how such diseases arise and suggest new strategies for therapy. A significant hurdle to this use and most uses of stem cells is that scientists do not yet fully understand the **signals** that turn specific genes on and off to influence the differentiation of the stem cell.

Human stem cells could also be used to test new drugs. For example, new medications could be tested for safety on differentiated cells generated from human **pluripotent** cell lines. Other kinds of cell lines are already used in this way. Cancer cell lines, for example, are used to screen potential anti-tumor drugs. But, the availability of pluripotent stem cells would allow drug testing in a wider range of cell types. However, to screen drugs effectively, the conditions must be identical when comparing different drugs. Therefore, scientists will have to be able to precisely control the differentiation of stem cells into the specific cell type on which drugs will be tested. Current knowledge of the signals controlling differentiation fall well short of being able to mimic these conditions precisely to consistently have identical differentiated cells for each drug being tested.

Perhaps the most important potential application of human stem cells is the generation of cells and tissues that could be used for **cell-based therapies.** Today, donated organs and tissues are often used to replace ailing or destroyed tissue, but the need for transplantable tissues and organs far outweighs the available supply. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including Parkinson's and Alzheimer's diseases, spinal-cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis.

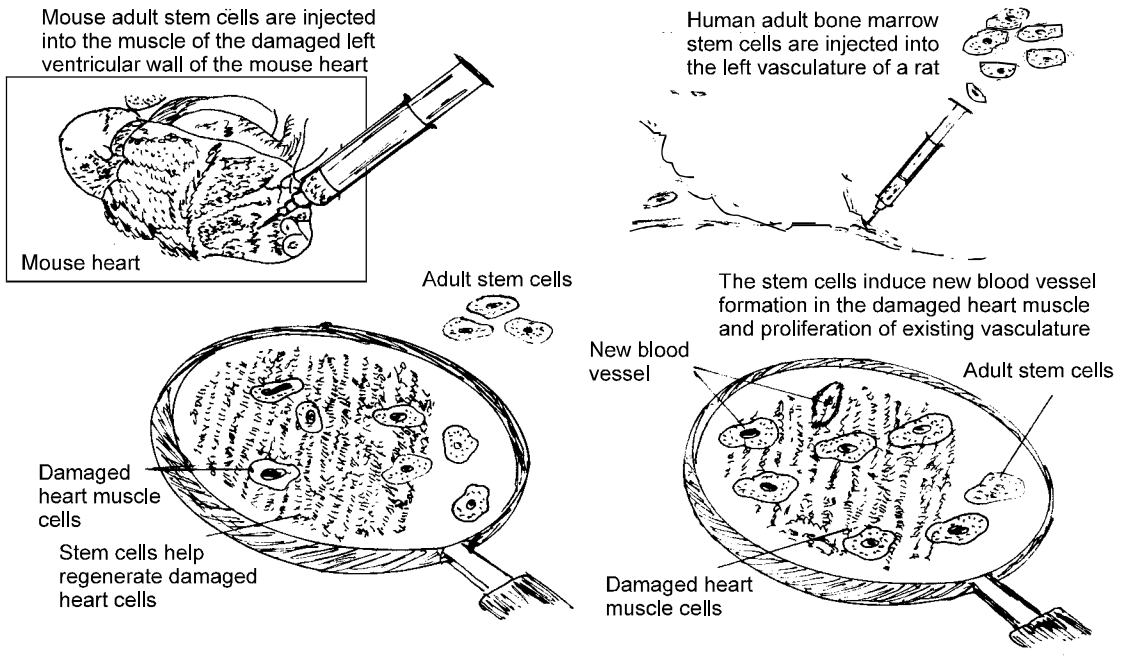


Fig. 4.4. Heart muscle repair with **adult stem cells**.

For example, it may become possible to generate healthy heart muscle cells in the laboratory and then transplant those cells into patients with chronic heart disease. Preliminary research in mice and other animals indicates that bone marrow stem cells, transplanted into a damaged heart, can generate heart muscle cells and successfully repopulate the heart tissue. Other recent studies in **cell culture** systems indicate that it may be possible to direct the **differentiation** of embryonic stem cells or adult bone marrow cells into heart muscle cells (Fig. 4.4).

In people who suffer from type I diabetes, the cells of the pancreas that normally produce insulin are destroyed by the patient's own immune system. New studies indicate that it may be possible to direct the differentiation of human embryonic stem cells in cell culture to form insulin-producing cells that eventually could be used in transplantation therapy for diabetics.

To realize the promise of novel cell-based therapies for such pervasive and debilitating diseases, scientists must be able to easily and reproducibly manipulate stem cells so that they possess the necessary characteristics for successful differentiation, transplantation and engraftment. The following is a list of steps in successful cell-based treatments that scientists will have to learn to precisely control to bring such treatments to the clinic. To be useful for transplant purposes, stem cells must be reproducibly made to:

- proliferate extensively and generate sufficient quantities of tissue;
- differentiate into the desired cell type(s);
- survive in the recipient after transplant;
- integrate into the surrounding tissue after transplant;
- function appropriately for the duration of the recipient's life;
- avoid harming the recipient in any way.

Also, to avoid the problem of immune rejection, scientists are experimenting with different research strategies to generate tissues that will not be rejected.

To summarize, the promise of stem-cell therapies is an exciting one, but significant technical hurdles remain that will only be overcome through years of intensive research.

ETHICS INVOLVED IN STEM-CELL RESEARCH

Stem cells show potential for many different areas of health and medical research, and studying them can help us understand how they transform into the dazzling array of specialized cells that make us what we are. Some of the most serious medical conditions, such as cancer and birth defects, are caused by problems that occur somewhere in this process. A better understanding of normal cell development will allow us to understand and perhaps correct the errors that cause these medical conditions.

Research on one kind of stem cell—human embryonic stem cells—has generated much interest and public debate. Pluripotent stem cells (cells that can develop into many different cell types of the body) are isolated from human embryos that are a few-days old. Pluripotent stem cell lines have also been developed from fetal tissue (older than 8 weeks of development).

As science and technology continue to advance, so do ethical viewpoints surrounding these developments. It is important to educate and explore the issues, scientifically and ethically.

(*a*) *Humanitarian-Hopes*

Powerful motivation for setting our minds to this task comes from the vision of scientists about what regenerative medicine might accomplish with stem cells derived from embryos.

Shortly after the discovery in 1998, of ways to nurture embryonic stem cells in the laboratory, the Director of the National Institute of Health, Harold Varmus, M.D., described the promise of this frontier in testimony before Congress. The embryonic stem cells of which Dr. Varmus spoke differ from the stem cells of developed humans (the latter often called "adult" stem cells). Embryonic stem cells possess the attribute of *pluripotency,* which is to say that they may issue in more than one cell type. Cells in the developed human, so far as is known, are not pluripotent. More information about the scientific promise of pluripotent embryonic stem cells may be learned from resources on human embryonic stem cells collected by the University of Wisconsin.

(*b*) *Moral Debate Concerning Embryonic Stem Cell Research*

Our task is to decide how we should act toward an embryo, and whether we should recognize, as we do among adults, distinctions between embryos of various types and in various circumstances. We immediately encounter the question of what beings we should classify as "persons" for purposes of the duty not to kill persons. Answering that question with the view that not every embryo should be classified as a person for purposes of that duty, the Protestant theologian Ronald Cole-Turner, M. Div., Ph.D., has offered a Christian moral defence of humanitarian embryo use.

In contrast, Edmund D. Pellegrino, M.D., of Georgetown University states a Catholic case against embryo use. As is well known, the official teaching of the Holy See of the Roman Catholic is unequivocal in its opposition to the use of embryos as means. For one who holds that we should treat every embryo as a person for purposes of the duty not to kill, embryo-destructive experiments could gain justification only if it were argued that it is sometimes permissible to kill some persons in order to help other persons, and that is an uphill argument within any moral view. But the official teaching of the Holy See is not the only interpretation of Catholic tradition. Margaret Farley, Ph.D., of Yale University explains that in history and in present theological discussion, there is more than one Catholic line of reasoning, including a strong Catholic moral defense of humanitarian embryo use. For one who concludes that we are not obliged to refrain from using embryos that will never enter a womb, embryonic stem cell research is a case of fostering a worthy end by using only nonpersons as means.

USE OF CELL-CULTURES AS ALTERNATIVES TO USE OF ANIMALS

Alternatives to use of animals are tests and procedures that incorporate replacement, reduction or refinement of animal use commonly referred to as three Rs. The concept of alternatives was first defined by WMS Russell and Rex Burch in their book entitled "The Principles of Humane Experimental Technique" published in 1959. The original definition given by the authors is as follows:

"Replacement means the substitution for conscious living higher animals of insentient material. ***Reduction*** means reduction in the numbers of animals used to obtain information of given amount and precision. ***Refinement*** means any decrease in the incidence or severity of inhumane procedures applied to those animals which still have to be used".

However, in the recent years the term alternative techniques has come into common usage with different meanings to different people. To many biomedical researchers, it refers to those which can be used in addition to the more traditional animal models. On the other hand some people refer the term alternative to those techniques, which can entirely replace the use of animals. Significant advances in the field of scientific research particularly molecular

biology and information technology have helped in the development of alternative techniques in the past two decades.

Alternative techniques and approaches, addressing the broad issues of three Rs are explained below with some specific examples.

REPLACEMENT

Alternatives which replace animal models could be broadly classified into the use of living systems, nonliving systems and computer simulation.

Use of Living Systems

(*a*) *In vitro techniques* : The most commonly recognized non-animal living systems are *in vitro* systems such as cell, tissue, and organ cultures. These *in vitro* systems isolate the system under study from the rest of the organism and are ideal for mechanistic investigations where it is desirable to avoid the confounding effects of systemic influences such as hormones. This can, however, be a disadvantage when these external factors have a crucial effect on the question being studied. These *in vitro* systems techniques are not seen as absolute replacement but only a relative replacement alternative, because they require freshly-obtained animal cells and tissue. However, even when freshly-isolated material is required, the animals are used more economically, because a single animal will provide tissue for a number of cultures.

The use of cell cultures can be more economical than the use of whole animals, once the necessary investment has been made to obtain the required experience and expertise. Cell culture studies can often be carried out in multi-well plates in order to enable data collection to be partially or fully automated. Primary cell cultures are produced from fresh tissue which has been disrupted so as to obtain individual cells. These cultures are fairly easy to set up, and they start with the advantage that they contain normal cells with all the characteristics that determine their specialised functions in the tissue of origin. However, they can only be maintained for a limited period of a few days, or perhaps weeks, and they tend lose their functional capacity with time. This means that further fresh tissue is constantly required and that the cultures cannot be used for long-term studies.

As compared to primary cell cultures, cell line cultures consist of cells which can keep on growing indefinitely. These cells are often derived from human or animal tumors, and some have been maintained for decades. They may under go transformation, which makes them insensitive to the control mechanisms that limit the number of times that normal cells can divide before dying. Cell lines can be bought as required, and a stock can be kept frozen in liquid nitrogen. They are widely used, because they are easy to maintain and do not require the use of tissue. However, it has not been possible to produce cell lines from every type of tissue. A further disadvantage is that the cells are abnormal in many ways and in some cases, they show no resemblance at all to normal cells from the tissue of origin. Efforts have also been developed embryonic stem cell lines which remain undifferentiated until induced to differentiate by a change in culture conditions. They are being investigated for their potential in teratogenicity testing and are also being used for gene knock-out studies to identify the role of defined genes. Through the introduction of viral oncogenes into primary cells, it is possible to produce immortalised cell lines which maintain the characteristics of differentiated cells but can be cultured for much longer.

Cell lines can be genetically engineered in a number of ways, for example genes can be introduced to obtain the expression of receptors on the cell surface, shuttle vectors can be introduced as target DNA for genotoxicity studies, and human genes can be inserted into an animal cell line to give it the enzymatic capability of human tissues.

The use of tissues or their fragments has also been attempted to replace the use of whole animal. For example, very thin slices of liver and kidney can be used to study the possible effects of drugs on these organs. Sometimes the tissue making up one part of an organ is cultured separately, for example the proximal tubules of the kidney. These systems are still economical in their use of animals and human tissue obtained after surgery may also be used in some cases. However, these cultures have a limited life span and a high level of technical skill is required to set up and maintain them. In some cases, three-dimensional tissue equivalents may be used instead of tissue cultures. These are systems in which it is possible to mimic tissue architecture by culturing cells on an artificial support matrix. A number of human skin equivalents have been developed, and work is in progress on tissue for various types of research and human placenta is one of them. However, whenever human tissue is used it can be difficult to obtain, store and distribute. Also it requires greater precautions to avoid risk arising due to presence of viruses (*e.g.,* HIV/AIDS). Establishment of tissue banks for human tissue that is unsuitable for transplantation can solve the problems of its supply.

Organ cultures have the advantage of enabling all the interactions which take place within the organ, and they are extensively used in pharmacological studies. However, they are difficult to maintain, short-lived, and use many animals, because one animal can only provide one organs (or two in the case of kidneys).

It may be noted that although, intercellular and intracellular interactions that can be studied are more close to those in whole animals as the level of anatomy increases *i.e.,* in cells, tissues and organs (Fig. 4.4), but it is difficult to maintain the tissue and the organ cultures in the laboratory as compared to cell cultures. Therefore, the cell culture techniques are most commonly used especially for monoclonal antibody production, virus vaccine production, vaccine potency testing, screening for the cytopathic effects of various compounds and studying the function and make up of cell membranes. The potential uses of *in vitro* techniques are almost limitless and will continue to expand as more is learned about the various organs and their component tissues and cells, and as the technology of maintaining *in vitro* environments improves.

(*b*) *Invertebrate animals* : Invertebrates represent over 90% of known plant species on the earth. Although their body structure is quite different to humans than as compared to verteb-rates body's structure, invertebrate anatomy, physiology, biochemistry and other metabolic functions can be used to replace the more commonly used laboratory animals. An invertebrate which has long been used in biomedical research is the fruit fly, *Drosophila melanogaster* — a classic model for the study of genetics. This species also can be used for detecting mutagenicity, teratogenicity and reproductive toxicity. The marine invertebrates represent different species which have not been widely investigated. However in neurobiology a number of different marine species have been well characterized and used to study the physiology of the nervous system.

(*c*) *Microorganisms* : The microorganisms represent a third system, which has been used to replace traditional animal models. The Ames mutagenicity/carcinogenicity test uses *Salmonella typhimurium* cultures to screen compounds that formerly required the use of animals. This test has been validated and accepted for screening purposes in regulatory toxicology. Similarly, the Litmus amoebocyte Lysate (LAL) test for endotoxins has also been validated and accepted for certain regulatory purposes to detect the presence of embryogenic fever-inducing endotoxins. A host of microscopic protozoans and metazoans have been used in biomedical research.

The advantage of using microorganisms include their repair division and growth body temperature which helps in multi-generational studies in a short period of time. They are also cost-effective in terms of storage, upkeep and maintenance. However, the major disadvantages is that they are unicellular organisms and the interaction of cells cannot be studied.

Use of Non-living Systems

The non-living systems used as alternative involve the use of physicochemical, analytical and molecular techniques and *in silica* systems.

(*a*) *Physico-chemical methods*: Physico-chemical methods are extensively used in initial ages of various screening studies. For example, pH and partition coefficient in combination with structure-activity relationships help in predicting the likely biological effects of chemicals. The commercial Ocular Irritation Assay System uses a proprietary reagent solution that is com-posed of proteins, glycoproteins, lipids and low molecular weight components that self-associate to form a complex macromolecular metric. The potential of a chemical to irritate the eyes is predicted by the extent to which it will coagulate the reagent. Many cosmetics companies use this system to screen out potential irritants without testing them in animals.

Immuno-chemical techniques use the binding capacity of highly-specific antibodies to seek out minute quantities of antigen. A classical example of this technique can be demonstrated by the currently used techniques for identifying bacterial toxins. Toxin identification previously required the injection of as many as several hundred mice with supernatant from cultures of suspected contaminating bacteria. These new antibody techniques save animals and speed up confirmation of a tentative diagnosis. By adding a colour marker to the enzyme-linked immunosorbent assay system (ELISA), the whole process becomes a commercially available test kit such as those used in home pregnancy detection.

(*b*) *Molecular methods*: Molecular methods as an alternative are based on studying the molecular interaction of test compound with DNA. For example, technology to rapidly analyse DNA from patients and identify genes that predispose individuals to fibrosing lung disease is an alternative to modeling the illness in animals such as genetically-modified mice.

The recent application of molecular biology to toxicity testing of pharmaceuticals has enabled predictions of safety using *in vitro* systems and high throughout screening systems as animal alternatives. These screening systems can be automated to provide fast cost-effective and more ethical approaches to toxicity screening.

A high-throughout screening (HTS) system consists of a variety of *in vitro* assay systems or other such platform technologies (such as yeast-based reporter gene assays, and a variety of receptor-binding and transcription activation assays using established mammillaria cell lines including human cells for identifying endocrine disrupter compounds often integrated with softwares to screen compounds as per the selected assay format. It is commonly used in negative selection of compounds *i.e.,* to screen out the compounds not matching the defined assay parameter. High throughout screening assays normally uses 96-well format plates formats but attempts are made for developing assay formats with higher plate density *e.g.,* 384 and 1536-well formats. These new approaches offer potential for making significant advances over existing screens in speed, high-throughout capability, sensitivity, reproducibility, and reduction in animal usage in a screening and testing program of new chemical entities for treatment of various diseases.

(*c*) *Use of computer simulation*: Mathematical and computer models can effectively complement animal experimentation. In fact, the use of computers in biomedicine is increasing as more biological process are understood and converted into mathematical forms. In order for

a biological phenomena to be adapted to a computer model, the basic processes must be expressed in a mathematical formula. Once a formula is developed then an enormous number of variables can be introduced and swiftly processed.

Computer models enable scientists to predict the way in which an organism may respond to varying levels of exposure to a certain chemical, and to design better experiments to actually determine the response in a living animal. For the most part, data in computer-based predictive systems are derived from the results of animal studies. Thus, the predictability is only as good as the animal data on which it is based.

Developments in computer modeling and systems for the prediction of biological activity and toxicity have already revolutionized the process of drug discovery and development, by eliminating the need to use animals for pre-screening of almost limitless numbers of potential drug candidates. For example, the protease inhibitors that are a key part of AIDS triple therapy were developed very quickly through the use of powerful computers which analysed the viral enzyme and predicted the kinds of chemicals that would block its action. This approach is now being used to target other stages of the AIDS virus cycle.

Application of computer models screening tools and commercial databases available for use by pharmaceutical industry ranges form toxicity predictions (quantitative structure function relationship) and ADME predictions, comparison and analysis of protein/DNA sequences, identification and prioritization of drug targets, high throughput screening, drug-drug interaction, convert gene sequence into 3-D protein structure and vice versa.

Computer simulations and multi-media presentations are often used to replace the use of animals in education. In order to achieve this, a huge amount of data, usually from *in vitro* studies, has to be collected and integrated into the program.

Computers also permit better data management. Computer-assisted data banks allow greater accessibility of experimental results to scientists in laboratories all over the world, thus reducing the need for test duplication. More recently, new technologies powered by computers, such as nuclear magnetic resonance spectroscopy, make it possible to observe biological phenomena that previously could only be inferred.

USE OF ANIMALS FOR RESEARCH AND TESTING

Introduction

There are 4 reasons why animals are used in research:

1. The principles of anatomy and physiology are true for humans and animals, especially mammals. Once scientists learned that animals were similar to humans, in physiology and anatomy, it became preferable to use animals rather than humans for preliminary research.

2. Certain strains or breeds of animals get the same diseases or conditions as humans. “Animal Models” are frequently critical to understanding a disease and developing appropriate treatments.

3. Research means introducing one variable and observing the results of that one item. With animals we can control their environment (temperature, humidity, etc.), and shield them from disease or conditions not related to the research (control their health). Although human and animals get the disease they may be the subject of a research investigation, the different life styles or living conditions make them poor subjects until preliminary research under controlled conditions has been done.

4. We can use scientifically-valid numbers of animals. Data from one animal or human is

not research; it is a case study. To scientifically test a hypothesis, an adequate number of subjects must be used to statistically test the results of the research.

Some individuals claim that we should use human or animals that have a disease to study that disease. Certainly, epidemiological studies (tracking the occurrence of a disease or condition) have provided many important insights into the cause of a disease or a condition, especially when an environmental aspect is responsible. As noted earlier, the study of a disease is severely hindered or not possible when the research subjects have been/are exposed to a variety of environmental factors.

It is important to note that, according to the American Medical Association, humans are the most frequently used animal in research. However, research studies conducted on humans follow preliminary studies conducted in animals. These animal studies make human studies a reasonable risk. The animal studies are not a guarantee of success, but they do tell us that the human research has a reasonable probability of success.

How are Animals Used in Research ?

CSIRO uses animals in research in a number of ways, as described below :

(*a*) *Ecological Studies*

The use of animals in ecological studies is usually limited to observation or capture-mark-release of free-living animals to identify what species and how many animals are present in a particular habitat. In capture-mark-release, reptiles and small mammals are caught in pit fall traps or other small enclosure traps. The information required for each animal is noted—species, sex, breeding status, and so on. The animal is marked to identify that it has been caught and counted, and then released at the point of capture. A small number of animals are retained as voucher specimens or blood sampled for DNA testing.

(*b*) *Laboratory Studies*

Laboratory animals such as rats, rabbits and guinea pigs are used by CSIRO for studies related to farm animals. Others are used in studies relating to human health such as studies that explore the role of diet and nutrition in the prevention of diseases, like cancer and cardiovascular disease.

Many of these animals are painlessly killed to provide biological materials such as blood and tissue for test-tube (*in vitro*) studies that focus on the cellular and molecular level rather than on the whole animal.

Rabbits are often used to produce antibodies to help diagnose disease in other animals, and to create new vaccines to protect animals against disease. These rabbits rarely show signs of sickness or discomfort when they are used in this way.

CSIRO continues to investigate new methods using gene technology to produce antibodies that could replace the use of laboratory animals.

(*c*) *Livestock Health*

The study of infectious disease often requires the experimental infection of animals. In order to control a new disease (and new ones arise regularly), it is necessary to know what systems of the body are involved, what other species may be susceptible, and how the disease spreads.

To examine the effectiveness of vaccines or other treatments that may be produced, an animal trial is eventually required. Animal use, however, has been reduced over recent decades, as laboratory techniques are now able to do much of the work before animal research is necessary.

Test-tube techniques or computer simulations are often useful, but cannot provide all the information needed to develop and trial an effective vaccine. Comparing the on-farm outcomes in vaccinated and unvaccinated animals, such as cattle and sheep, is the only way to provide crucial information.

Livestock Productivity

Animal-based research projects that are aimed at improving livestock productivity often involve large number of animals. These animals receive no or few experimental treatments other than the husbandry practices that farm animals would usually receive. For example, in a project to select sheep resistant to internal parasites, the faeces it over 6,000 sheep were collected and examined for worm eggs and larvae.

Principles Guiding Animal Research

CSIRO considers the welfare of animals, whether domestic or native, to be one of its most important missions, and much of our science is directed at improving it.

We care about the health, well-being and welfare of animals, and we are sensitive to public and industry expectations that they be treated humanely, kindly and without undue stress.

We aim to meet the highest standards of animal care in all we do, and to remain sensitive to changing public values and attitudes on this issue.

CSIRO, in consultation with its Animal Ethics Committees (AECs), follows the '3Rs' of animal welfare. They are:

Replacement of animal research with other research techniques that do not repair animals wherever possible.

Reduction of the number of animals used in any research.

Refinement of animal research to ensure the optimum quality of life for those animals involved in research.

Animal disease studies may cause pain or discomfort for some animals. Prompt steps are taken to relieve this, but if seriously affected, animals are humanely put down as soon as possible. The overall aim of animal health research is to prevent Australia's animals experiencing pain and suffering from disease.

Regulation of Animals Experiments

By law, every Australian research organisation using animals in experiments must establish an Animal Ethics Committee (AEC). Each AEC is required to include members with specific backgrounds–veterinary science, animal welfare, animal experimentation, and no experience in animal experimentation. At least two members must be independent from the organisation undertaking the research.

Any research proposal must be approved by the AEC before it can proceed. Scientists must be able to show that the research is beneficial, and that it cannot be undertaken without using animals. The Committee also ensures that excessive animal use does not occur, distress to the animal is prevented or minimised throughout the experiment, and that the quality of life of the animal is acceptable.

CSIRO's Animal Ethics Committee meet several times a year to consider new research proposals, and monitor ongoing experiments.

Scientists at CSIRO also follow the *"Australian Model Code of Practice for the Care and Use of Animals for Scientific Purposes"*. The code was produced jointly by the Standing Committee on Agriculture and Resource Management (SCARM), together with the National

Health and Medical Research Council (NHMRC), Australian Research Council (ARC) CSIRO, and the Australian Vice-Chancellors' Committee (AVCC). These bodies are all signatories to the Code.

The Code of Practice is intended as a guide for people responsible for the welfare and husbandry of a range of animals, as well as AEC members. The Code is kept under review to take account of advances in the understanding of animal physiology and behaviour, changes in animal husbandry and their relationships to the welfare of animals.

The Code covers topics such as the acquisition and care of animals in breeding and holding areas, wildlife studies, and the care and use of livestock of scientific and teaching activities. For example, it specifies that animal accommodation should be designed and managed to meet species-specific needs, and that animals must receive appropriate uncontaminated and nutritionally-adequate food.

Initiatives of the CSIRO's Animal Ethics Committees

CSIRO's Animal Ethics Committees have actively encouraged:

- Involvement of a biometrician in development of all protocols to ensure that the minimum number of individual animals are used to acquire meaningful data.
- Minimising the impact of studies on individual animals by provision of environmental enrichments such as toys and novel methods of feeding, and by defining humane endpoints for each study.
- The use of alternatives to animal research, such as growing tissue cells in a nutrient medium to produce cellular proteins that are used in disease defence, instead of using more mice.
- Creation of Standard Operating Procedures for scientific staff, that advice the best way of performing certain common procedures involving animals, in the interests of animal welfare and therefore good quality science.
- Publication of Standard Operating Procedures for scientific staff, that advise the best way of performing procedures on animals, in the interests of their welfare and good quality science.
- The inclusion of a section on Wildlife Studies in the *Australian code of practice for the care and use of animals for scientific purposes, 6th edition 1997.*
- Modification of pitfall traps to provide protection of trapped animals from heat, dehydration, flooding and predation by other animals during the period that they are in the traps.
- Research into the use of analgesics in animals being used in studies of disease processes.

ANIMAL CLONING

While the technique of cloning has changed dramatically over the years, the basic principle remains the same. Take a blood clotting factor protein we would like to clone in a cow as an example. Essentially, the gene for the factor would be linked to a *promoter* specific for a milk protein. This promoter is responsible for ensuring that the gene is only expressed in the milk of the animal. Many copies of this promoter-gene combo are then introduced into a cow's egg, which is allowed to develop in a surrogate animal (see Fig. 4.5). A technique called 'Pronuclear injection' is used to do this and involves injecting the DNA directly into fertilized eggs using a very fine glass needle (transfection).

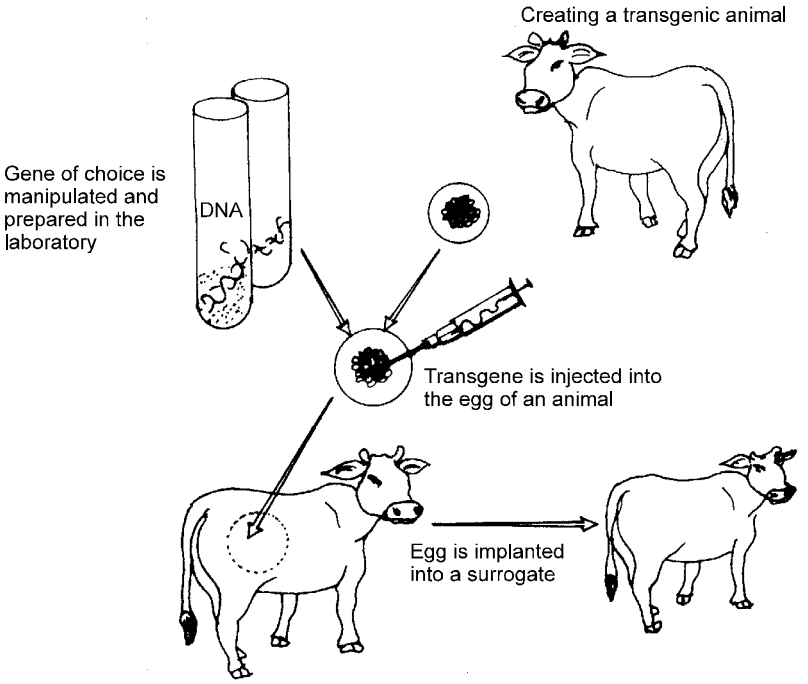


Fig. 4.5. **Creating a Transgenic Animal.** To create transgenic animal, in brief, the gene of choice manipulated and prepared in the laboratory, transgene is then injected into the egg of an animal which is implanted into the surrogate.

However, pronuclear injection is very unreliable. This is due to DNA uptake and integration into the genome of the egg cell being a very rare event, typically resulting in 1 to 5 transgenic animals out of every 100 being born. Dolly the sheep, the first animal cloned by pronuclear injection, was the result of one success out of 277 eggs. Another Biotech company, PPL Therapeutics, took several years just to produce a flock of 600 transgenic sheep.

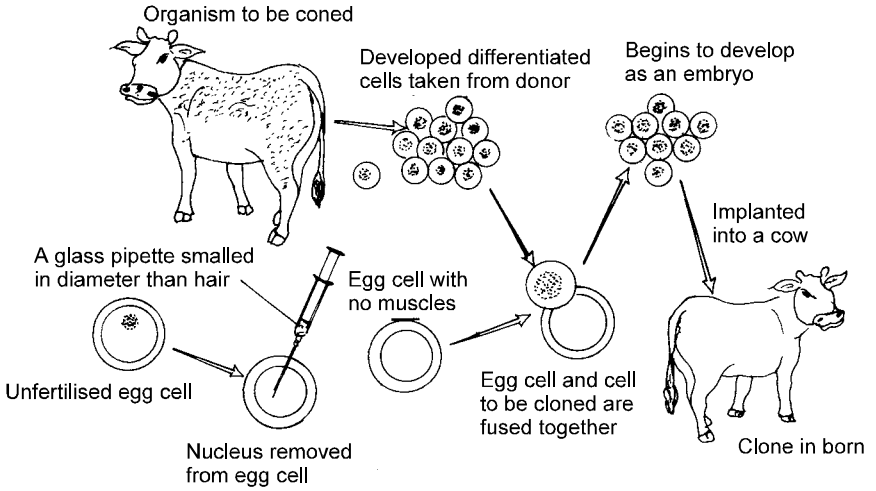


Fig. 4.6. **Nuclear Transfer Technology.** One method of cloning animal nuclear transfer involves removing the nucleus from a donor animal planting it into an egg cell that has had its nucleus previously removed.

It was obvious that if pronuclear injection were the only animal cloning technique available, pharming would not be a feasible option. This problem has been solved by a new technique called 'nuclear transfer', which solves the low percentage of transgenic offspring by selecting for eggs that have cloned genes integrated into the egg's genome before it is implanted into the surrogate (see Fig. 6). Essentially, cells are transfected as before, with the addition of a gene that makes the egg resistant to an antibiotic if it is expressed properly. This allows for the selection of only those cells that properly express the antibiotic resistance gene, and in conjunction the gene of interest. The nucleus of these cells are then removed and transferred to an egg to allow fusion with the nucleus. Since all the eggs contain the transgene, virtually 100% of the offspring will be transgenic animals.

ETHICS AND ANIMAL CLONING

Should this be allowed ethically? To look at this, here are several possible criteria—unnaturalness, diversity, fundamental concerns, animal welfare and commodification.

Is it Unnatural ?

Many people say that cloning farm animals would be unnatural. Whereas in the plant kingdom cloning is a fairly common phenomenon, there are few animal examples and none in mammals or humans. Should we then respect this biological distinction, or should we celebrate our human capacity to override such limitations? It is hard to argue in an absolute sense that anything is unnatural, when so little remains around us that we might justifiably call natural, and nature itself is in constant motion. Yet many believe some technological inventions are now going too far to remain in tune with what we perceive "natural" to mean, despite how much we have intervened in nature to date. Is cloning animals a point to draw a line?

Would it Narrow Genetic Diversity too far ?

This brings us to the question of diversity. One of the fundamental rules of selective breeding is that you must maintain a high enough level of genetic variation. The more you narrow down the genetic "pool" to a limited number of lines of, say, animals for meat or milk production, the more you run risks of problems from in-breeding. If that is the case with breeding, how much more is it true of cloning, where genetic replicas are involved. This means there are pragmatic limits to how useful cloning would be, but beneath the pragmatics there lies a deeper ethical concern. Does this reflect something fundamental about the nature of things?

Is there a Fundamental Ethical Concern ?

This is something for which Christian theology provides some insights. For the Christian, the world around us is God's creation, and one of its most characteristic features is variety. The biblical writers make repeated allusions to it, painting striking pictures of a creation whose very diversity is a cause of praise to its creator. It could be argued that to produce replica humans or animals on demand would be to go against something basic and God-given about the very nature of higher forms of life. Where God evolves a system of boundless possibilities which works by diversification, is it typically human to select out certain functions we think are the best, and replicate them? Deliberate cloning aims at predictability, replication, in order to exercise control, whose centralised, even totalitarian approach contrasts with God's command to animals and humans to "be fruitful and multiply". In the limit this argument would mean that cloning would be absolutely wrong, no matter what it was being used for. This intuition runs deep in many people. But there are also questions of scale and intention to consider.

Justifiable Uses of Cloning

Cloning animals might be acceptable in the limited context of research or where the main intention was not the clone as such but growing an animal of a known genetic composition, where natural methods would not work. Roslin's work to produce 'Poly' the transgenic-cloned sheep would be such a case, where the intention is not primarily to clone, but to find more precise ways of animal genetic engineering. Indeed, producing medically useful proteins in sheep's milk is one of the least contentious genetic modifications in animals, since the intervention in the animal is very small for a considerable human benefit. Careful scrutiny would be needed, to see that it was only applied to genetic manipulations that would be ethically acceptable, but that is a question we already faced before cloning.

Animal Welfare Concerns

We also need to be sure about the animal welfare aspects even of limited cloning. Questions have been raised about the number of failed pregnancies and unusually large progeny which appear to be resulting from Roslin's nuclear transfer experiments to date. While the suffering is not so great as to put a stop to this work, it is clearly necessary to understand the causes and establish whether the problems can be prevented, before the methods could be allowed for more general use. If after a reasonable time there seemed little prospect doing so, however, one would doubt whether it was ethical to go any further. This also points to the serious possibility that any attempt at human cloning could be extremely dangerous for both the clone and mother, and thus medically unethical, irrespective of wider ethical concerns.

HUMAN CLONING

To understand the cloning debate (and to distinguish cloning from genetic engineering, which many opponents fail to do) we need to understand:

(a) Reproductive cloning: creating a new organism from a single cell of an adult. The genes (but not the far less-important mitochondrial DNA) of the offspring are identical to the parent.

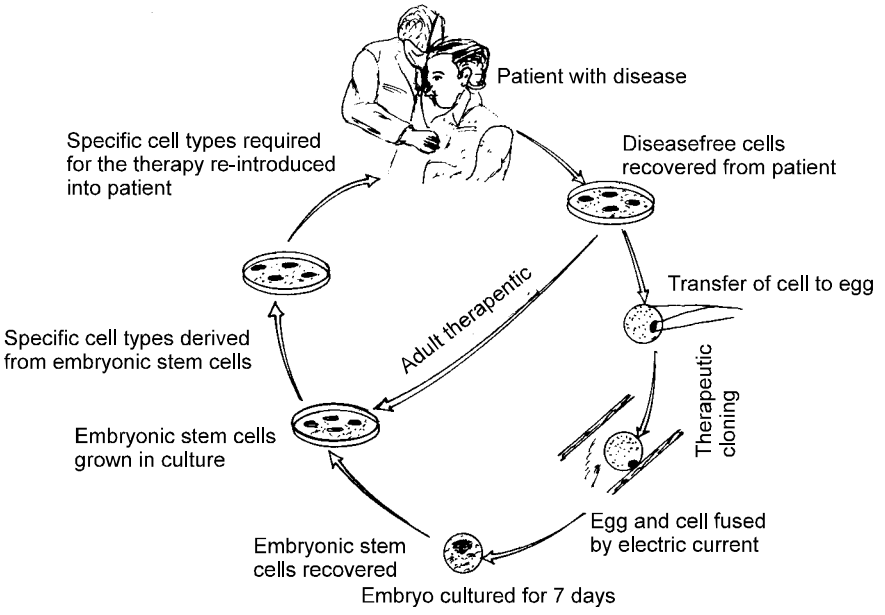


Fig. 4.7. Process of human cloning.

(*b*) ***Therapeutic cloning:*** creating embryos to supply embryonic stem cells as a source of spare parts to treat disease.

(*c*) ***Genetic engineering:*** changing genes in cells that will be transmitted to all offspring, was recently used to make pigs that many supply compatible transplant organs for people.

WHY CLONING HUMANS IS ETHICALLY UNACCEPTABLE?

Dr. Wilmut, the scientist involved, and his colleagues at Roslin have made it quite clear that they think that to clone humans would be unethical. The Human Fertilisation and embryology Authority agrees with the general public impression that to clone human being would be ethically unacceptable as a matter of principle. I and most people in the Church of Scotland would certainly agree that on principle, to replicate any human technologically is something which goes against the basic dignity of the uniqueness of each human being in God's sight. Christians would see this as a violation of the uniqueness of a human life, which God has given to each of us and to no one else. In what sense do we mean this ?

Some say that the existence of "identical" twins means that we should have no ethical difficulty over cloning, or that to object to cloning implies that twins are abnormal. This argument does not hold. Biologically, identical human twins are not the norm, but the unusual manner of their creation does not make them any less human. We recognize that each is a uniquely valuable individual. There are two fundamental between cloning and twinning, however. Twinning is a random, unpredictable event, involving the duplicating of a genetic composition which has never existed before and which at that point is unknown. Cloning would choose the genetic composition of some existing person and make another individual with the same genes. It is an intentional, controlled action to produce a specific known end. In terms of ethics, choosing to clone from a known individual, and the unpredictable creation in the womb of twins of unknown genetic nature belong to categories as different as accidental death is to murder. The mere existence of "identical" twins cannot be cited to justify the practice of cloning.

CONTROLLING SOMEONE ELSE'S GENETIC MAKEUP

Thus it is not the genetic identity that is the crucial point but the human act of control, and it is this element of control which provides the fundamental ethical case against human cloning. The biblical picture of humanity implies that we are far more than just our genes, or even our genes plus environmental influences, there is also our spiritual dimension, made in God's image, constituting a holistic notion of being, in which the relational element is as important as the individual. To be a person is to be in relationship. Hence, it is vital that the relational implications of technology are considered alongside the ontological. It is against this picture that most Christians would see it ethically unacceptable to clone human beings as a matter of principle. In so far as genes are a fundamental part of our make up, to choose to replicate the genetic part of human make up technologically is a violation of a vital aspect of the basic dignity and uniqueness of each human. By definition, to clone is to exercise unprecedented control over the genetic dimension of another individual. This is quite different from the control parents exert in bringing up our children. Whatever the parents do or do not do, it is inevitable that they have a profound effect on their children. No one exerts the level of control involved in preselecting a child's entire genetic make up except by a very deliberate act. Moreover, a child can reject any aspect of its upbringing, but it could never reject the genes that were chosen for it. Such control by one human over another is incompatible with the ethical notion of human freedom, in the sense of that each individual's genetic identity should be inherently unpredictable and unplanned.

INSTRUMENTALITY

Cloning raises a number of concerns arising from its consequences, of which instrumentality and risk are of special importance. To replicate any human being technologically is a fundamentally instrumental act towards two unique individuals – the one from whom the clone is taken and the clone itself. In nearly all the speculative ideas for cloning a human would use the clone as a means towards someone else's end. They would be created as clones for the primary benefit not of the individuals themselves but of some third party. This would be the case for cloning a dying child or parent to help those bereaved cope with the loss, or cloning an infant with a predisposition to leukaemia, as a source of bone marrow which would suffer less tissue rejection problems. These violate a basic ethical principle, that of create another human being other than primarily for their own sake. There is an important distinction in Christian theology, which admits an instrumental role for animals, to a limited degree, but prohibits it in humans. To clone a child with leukaemia to provide compatible bone marrow would treat the cloned sibling to that extent as means to an end, for the benefit of a third party, rather than for their own sake, and without their consent. Dorothy Werth cited the controversial US case where this was done through normal reproduction, but I would question whether the fact that it worked is justification enough. Again, it is rightly said that we have mixed motives for why we want children, but that does not justify treating a child as a means to an end.

INFERTILITY – AN EXCEPTION TO INSTRUMENTALITY

An exception to this objection would be the idea of producing a child from an infertile couple by cloning one of them. But this raises other problems. Instead of being the unique genetic product of both parents, the child is a copy of one of them. For many Christians this would be a denial of a basic relational aspect of reproduction, just as in the case of surrogacy. For an infertile couple to have a child by cloning one of them would not normally be thought of as an instrumental act, and might at first sight sound like a compassionate option to offer to childless couples. As observed above, however, there could be serious ethical problems, notwithstanding the anguish which childlessness brings to many couples. It would not be the biological child of both parents in the normal sense. For many this might be seen as taking the technological harnessing of the desire for a child one step too far, a means which is not justified by the end. The tendency is becoming to demand parenthood as my right, as though it were some moral absolute. We are losing the Christian understanding of children are a gift, not a right which we can presume that God or life should give us on demand.

PSYCHOLOGICAL EFFECT – IDENTITY AND RELATIONSHIP

There are a number of reasons why human cloning might be ruled out for the psychological dangers involved. No one knows what would be the effects on human identity and relationships of creating someone who is the twin of their father or mother, but born in a different generation and environment. Would the clone feel that he or she was just a copy of someone else who's already existed and not really themselves? Am I really someone else but put into a different womb? What will be my relationship to the one I was cloned from? No one can predict with any degree of assurance what the response would be. Presumably they would vary from person to person. I suggest there sufficient dangers for applying the precautionary principle should apply. In other words, even though one could not be sure how many people would suffer in this way, it would be wrong knowingly to inflict that risk on someone whose interests are being put first?

PHYSICAL RISK

Dolly took 277 attempts and nearly 30 failed pregnancies to get one success. To repeat the same thing on humans would be giving both the mother and the potential foetus an unacceptably high risk of damage. The basic science of fusing the cytoplasm and nucleus and reactivating the cell is very poorly understood. How many abnormal babies would have to be produced to get one right? There are sufficient unknowns about physical problems in pregnancy with cloned sheep and cattle to suggest that human cloning experiments would violate normal medical practice. Roslin researchers have said that there is no experiment that could be done to prove the safety of human cloning without causing serious risk to humans in the process. Then there are also unknown factors of ageing. How old is Dolly? Is she her age since her birth, or her age since birth plus the age of the tissue from which she was taken? No one knows what the effect of nuclear transfer on ageing processes.

SOCIAL RISK

Finally, human cloning would bring grave risks of abuses to human dignity and exploitation by unscrupulous people. We have already seen examples of people offering cloning services for large sums of money, when there is currently no reasonable prospect of delivery, and apparently regardless of the risks involved or, in the case of Richard Seed, the rule of law. It is also an open door for abuse, in the way that another individual, a group in society or even the state could exert undue control over an individual. If anyone ever did unfortunately clone humans, it is important to counter the suggestion from science fiction that they would be subhuman androids with human bodies but no souls. More seriously, some papers from an Islamic perspective seem to imply that if reproduction is by human artifice, it lacks the spiritual element. Some Christians think the same. I do not, however, see any grounds that a cloned child would be any less human than another child. Why would God fail to make the child fully “in His image” just because the manner of conception? There would need to be considerable safeguards to avoid the risk of stigmatization. It would be foolish to imagine that abuses could not occur.

Unit 5: Organs Transplantation in Human Beings

ETHICS IN XENOTRANSPLANTATION

INTRODUCTION

Transplantation represents a highly successful means of treating a variety of human illnesses. However, the number of transplants performed is limited by a shortage of human organs and tissues. Xenotransplantation, the transplantation of organs, tissues or cells from one species to another, if applied to man, would offer the possibility of a huge supply of organs, tissues and cells for transplantation thereby relieving the "chronic" shortage of human donor.

However, before xenotransplantation becomes a clinical reality, there are practical challenges that must be overcome. One is rejection, the process by which the body of the transplant recipient attempts to rid itself of the transplant. Another is to ensure the correct functioning, across species barriers, of the transplant in its new host. Also, there is the need to minimize the likelihood of the introduction of new infectious agents into the human population *via* the transplant.

In addition there are concerns about xenotransplantation that require theological, anthropological, psychological and ethical considerations, as well as an examination of legal issues and procedural matters.

BIOETHICAL ISSUES

Further investigation and clarification is needed for a wider bioethical analysis. The ethical evaluation of the practicability of xenotransplantation, in light of the current situation as summarized in the first part of this document, requires the consideration of a whole series of factors, some of which are derived from the general moral norms valid for all transplants, and others of which are more specifically related to xenotransplantation.

The Health Risk

As previously stated, one of the fundamental ethical questions that should be examined when judging the legitimacy of xenotransplantation is that of the *health risk* involved in such procedures. This risk is dependent on various factors which cannot always be predicted or assessed. Before going on, therefore, it may be useful to recall some general aspects of the ethics of risk.

Risk – understood as an unwanted or damaging future event, the actual occurrence of which is not certain but possible – is defined by means of two characteristics: the level of probability and the extent of damage. The probability of the occurrence of a certain damaging event in particular circumstances can be expressed as a risk percentage or as a statistical frequency. Furthermore, the presence or absence of certain chance factors of risk can sometimes alter the probability that a certain event will take place. The extent of the damage, in contrast, is measured by

the effects that the event produces. Naturally, a very probable risk is easily tolerated if the extent of damage associated with it is very small; on the contrary, a risk that causes a high level of damage, however improbable, gives rise to much greater concern and require greater caution.

It is important to distinguish between a *probable event* (event with varying degrees of probability) and an *event* that is only *hypothetical*; this latter is an event which is *not theoretically impossible* but which is so improbable as to require no change in behaviour or choices.

Together, these two criteria – probability and extent of damage – define the *acceptability* of the risk, as reflected by the *risk / benefit ratio.* Only when a risk can be concretely assessed it is possible to apply criteria for evaluating its acceptability.

Lastly, it is necessary to distinguish acceptability from what we can define as the *acceptance* of the risk, as defined by the reaction of the individual or of the general public to the existence of the risk. This is a response that has a significant subjective component, one which is not always completely thought out and which is influenced by culture, by the information available and how it is understood, by the way in which the information itself is communicated, and by common sensibilities.

In the absence of data that allow a reliable assessment of such a risk, greater caution should be used; this does not necessarily mean, however, that a total "block" should be put on all experimentation. Indeed, to move from ignorance to knowledge, from the unknown to the known requires the exploration of new approaches which in all likelihood, especially; during initial experimental stages, will not be without risks, at least potentially. In this situation, therefore, the imperative ethical requirements is to proceed by "small steps" in this acquisition of new knowledge, making use in experiments of the least possible number of subjects, with careful and constant monitoring and a readiness at every moment to revise the design of the experiment on the basis of new data emerging.

It is important to consider the distinction between *risk assessment* and *risk management*. To achieve an ethical assessment, both elements must be carefully examined.

This general discussion of the ethics of risk must now be applied to the specific case of xenotransplantation.

First of all, we note that there are issues connected with xenotransplantation, such as the probability of rejection and the increase in the probability of infection because of immunosuppressive therapies, about which some degree of knowledge already exists, although further study is necessary. The data which the scientific community already possesses, together with new data being gathered, can help to establish the threshold of risk that must not be crossed if a transplant operation to be considered morally acceptable.

More complex and uncertain is the assessment and evaluation of risks, connected to one specific aspect of xenotransplantation: the possible transmission to the recipient of infections arising from the xenotransplantation (*zoonoses*) by known or unknown pathogenic agents which are not harmful to the animal but which are possibly dangerous for man. Such infections could escape detection, with the consequent possibility of the spread of the infection to those having close contacts with the patient leading eventually to its being spread to the entire population.

Since clinical experience of xenotransplantation is quite limited and certainly insufficient to provide reliable statistics on the real probability of occurrences and spread of infections, any decision concerning clinical development of the new therapy can only be based on hypothesis. There is, therefore, an ethical requirement to proceed with the greatest caution.

When the moment for clinical application of xenotransplantation arrives it will be necessary to select patients carefully, based on clear and well-established criteria, and to monitor the

patient very closely and constantly. One must also contemplate the possibility of placing the patient in quarantine to prevent the epidemic spread of an infection. Arrangements for some kind of monitoring of those having close contacts with patient should also be made.

Moreover, during the experimental phase of clinical trials, patients should agree not to procreate because of the possible risk of genetic recombination that could affect the patient's germ cells. Sexual abstinence would also be necessary to avoid the venereal transmission of possible viruses. In the clinical application of xenotransplantation, psychology should also play an important role. It should address the probable repercussions that the recipient could undergo in their psyche (*e.g.,* because of the modification of one's "bodily schema") arising from the acceptance of a foreign organ, especially when it comes from an animal. In the post-transplant stage, psychology must also provide clinical support for the patient in the process of integration.

TRANSGENESIS

The use of organs from *engineered* animals for xenotransplantation raises the need for certain reflections on transgenesis and its ethical implications.

The term "transgenic animal" is used to indicate an animal whose genetic make-up has been modified by the introduction of a new gene (or genes). In contrast, the term "knock out" is used to designate those animals in which a given endogenous gene (or genes) is no longer expressed. In either case, such animals will express particular characteristics which will be transmitted to the offspring.

As we have already observed, the possibility of working out such genetic modifications, using genes of human origin as well, is normally acceptable when done in respect for the animal and for biodiversity, and with a view to bringing significant benefits to man himself. Therefore, while recognizing the *transgenesis* does not compromise the overall genetic identity of the mutated animal or its species, and reaffirming man's responsibility towards the created order and towards the pursuit of improving health by means of certain types of genetic manipulation, we will now enumerate some fundamental ethical conditions which must be respected:

1. Concern for the well-being of genetically-modified animals should be guaranteed so that the effect of the *transgene's* expression, possible modification of the anatomical, physiological and/or behavioural aspects of the animal may be assessed, all the while limiting the levels of stress and pain, suffering and anxiety experienced by the animal;

2. The effects on the offspring and possible repercussions for the environment should be considered;

3. Such animals should be kept under tight control and should not be released into the general environment;

4. The number of animals used in experiments should be kept to a bare minimum;

5. The removal of organs and/or tissues must take place during a single surgical opera-tion;

6. Every experimental protocol on animals must be evaluated by a competent ethics committee.

INFORMED CONSENT

In the ethical discussion on xenotransplantation, the subject of informed consent also deserves special attention.

Given the animal source of the organs which will be transplanted, this issues concerns only the recipient and, secondly, his relatives. At the outset the recipient should be given every information regarding his pathology and its prognosis, the xenotransplant operation and subsequent therapy, and the probability of success and the risks of rejection. Special attention should be paid to making sure that the patient is informed about the real and hypothetical risks of zoonoses, in light of current data, and about the precautions to be adopted in the case of infection (in particular the possible need for quarantine, which involves avoiding physical contact with others while the risk of contagion is present). The patient must also be informed about the need to remain under medical supervision for the rest of his life, so that the necessary constant monitoring following the transplant may be carried out. In addition, adequate information on possible alternative therapies to xenotransplant therapy should not be withheld.

This informed consent on the part of the patient should be understood as *personal.* For this reason, minors and those unable to give valid consent are to be excluded from the experimental phase.

However, if a patient incapable of giving valid consent should find himself in a previously unforeseen situation where there is danger of imminent death, recourse may be made to a legal representative (*e.g.,* in the hypothetical case of a *life-saving* xenotransplant as a temporary solution for a patient in a coma), provided that the medical procedures to be used offers a reasonable hope of benefit for the patient.

The patient's relatives should also be informed about what the transplant could entail regarding their contact with the patient and about the possible risks of contagion should an infection, as mentioned above, set in. In a strict sense, however, consent cannot be requested from them, since it is the patient who is ultimately responsible for the choices concerning his own health.

ALLOCATION OF HEALTH CARE RESOURCES

Xenotransplantation certainly represents a form of possible treatment requiring a great outlay of both health care resources and economic resources. For this reason, some people have expressed doubts about its ethical validity; given the large amounts of resources that it would take away from the other forms of therapeutic treatment and from other area of research, they consider both the uncertainty about its success and the risk entailed to be excessive. Faced with these doubts, it is important to remember that, even taken into due consideration the costs-benefits balance, the huge amount of health care resources used in this case is justified by the urgent need to try to save the lives of so many patients who would otherwise have no chance of survival.

It should also be added that as long as xenotransplantation on man remains at an experimental stage it should not be subject to the criteria applied to treatment in strict sense; rather it should be evaluated according to the criteria used for trials. Therefore, the foreseeable collective benefits that it may accrue in the future should also be taken into account. We do well to recognize here that the research into xenotransplantation which has taken place so far has also brought about greater medical knowledge in the area of allotransplantation.

PATENTABILITY AND XENOTRANSPLANTATION

Research on xenotransplantation has hitherto in large measure been carried out largely by private pharmaceutical companies which have committed substantial economic resources to this endeavour; they have also been providing financing to public institutions for the pur-

pose of obtaining better therapeutic results. It is therefore reasonable for them to expect an economic return on the investment made; one of the possible ways to do this is by acquiring patents.

From a formal point of view, there is no technical or legal obstacle standing in the way of the patenting *genetically engineered* animal organs intended for transplants. It should be emphasized however, that the norms drawn up by the European Community to regulate this matter could not, at the time they were being drafted, take into account the use of such organs for transplant from animal to man, since this therapeutic procedure had not yet been accomplished in clinical practice.

We therefore stress that, given the extraordinary financial commitment that has been made, now is the time to reconsider – or rather to be more precise about – the specific norms that apply.

We are aware of the broad debate underway on the basic question of whether the possibility itself of patenting living beings (even though genetically modified) or parts of them, especially when they contain genetic elements derived from humans (as is the case with animal organs genetically engineered for xenotransplantation into man), is ethically acceptable. We are also aware that there is a difference between a "discovery" (which cannot be patented) and an "invention" (which can be patented). Although it is our view that the transgenic animal as such – and all the more when they are used for transplantation into man – should be considered "nonpatentable", we nonetheless believe that it is not the purpose of present document to address this complex question directly.

Here, we shall limit ourselves to emphasizing that, whatever answer may be given to this basic question, it is always necessary — as a bare minimum — to guarantee respect for the fundamental right of every person to equitable access to the health care they may be needed, without discrimination and without being impeded by excessive costs. This applies above all else to accessibility to treatment. This objective — in the phyothetical case of patents connected with xenotransplantation, a procedure which should be viewed from a therapeutic standpoint— can be reached by making appropriate legal requirements apply (for example, the introduction of compulsory licences), thus allowing "production" at accessible prices which would hopefully be controlled by a supranational body specifically set up for this purpose.

ORGAN CULTURE

Not whole but pieces of organs can be cultured on artificial medium. For organ culture care should be taken to handle in such a way that tissue should not be damaged. Therefore, organ culture technique demands more tactful manipulation than tissue culture. The culture media on which organ is cultured are the same as described for cell and tissue culture. However, it is more easy to culture embryonic organs than the adult animals. Methods of culturing embryonic organ and adult organs differ. Besides, culture of whole or part of animal organ is difficult because these require high amount of O_2 (about 95%). Special serum-free media (*e.g.,* TS) and special apparatus (Towells type II culture chambered) are used for adult culture. In addition, the embryonic organs can be cultured by applying any of the following three methods:

(*i*) *Organ culture on plasma clots*

A plasma clot is prepared by mixing five drops of embryo extract with 15 drops of plasma in a watch glass placed on a cotton wool pad. The cotton wool pad is put in a petridish. Time to time cotton is moistened so that excessive evaporation should not occur. Therefore, a small piece of organ tissue is placed on the top of plasma clot present in the watch glass. In the modified technique the organ tissue is placed into raft of tense paper or rayon. The raft makes easy to transfer the tissue, excess fluid can also be removed.

(ii) Organ culture on Agar

Solidified culture medium with agar is also used for organ culture. The nutrient agar media may or may not contain serum. When agar is used in medium, no extra mechanical support is required. Agar does not allow to liquefy the support. The tumours obtained from adults fail to survive on agar media, whereas embryonic organs grow well. The medium consists of ingredients: agar (1% in basal salt solution), chick embryo extracts and horse serum in the ratio of 7:3:3 respectively.

(iii) Organ culture in liquid media

The liquid media consist of all the ingredients except agar. When liquid media are used for organ culture, generally perforated metal gauze or cellulose acetate or a raft of lens paper is used. These possibility provides support.

ETHICAL ISSUES

Ethical issues concerning xenotransplantation include animal rights, allocation of resources, and distributive justice. In addition to obtaining consent for xenotransplants from individual patients, consent is also necessary from the populace, given the public health risks.

ANIMAL RIGHTS

The genetic make-up of larger primates is about 98 percent identical to humans. Opportunities exist to make medical breakthroughs by overcoming species' immune barriers in ways that blur ethical boundaries. *The British Medical Journal* recently published a letter on xenotransplantation from *Neville Goodman*, a physician. He is outraged that expensive high technology treatments like this are going forward at a time when political will is lacking to make basic medical resources available in third world. With indignation, he quotes a researcher raising baboons for xenotransplant organs, who says her baboons "are treated better than some people in third world countries", as if proper treatment of the monkeys ends any ethical questions about xenotransplantation. It seems that scientists are unclear and in profound disagreement among themselves as to where the lines should be drawn.

Although some researchers prefer to work with primates, such as baboons or chimpanzees, Jane Goodall makes a very compelling argument against using chimpanzees in any laboratory research. Her observations of their social behavior over a period of 29 years prove their capacity not only for emotional depth, but also for altruistic behavior. Goodall shows that capturing infant chimps by killing their mothers has contributed to their endangered status, because young monkeys separated from their mothers do not thrive or become prolific breeders.

Respect for the rights of all beings is a tenet of the world's major religions, and it gives the animal rights movement the support of serious long-standing tradition. Daniel Rothman warns against taking the message of animal rights advocates lightly. He points out that what is most deplorable is unnecessary, frivolous use of animals that creates suffering. "The fear of being casual with life", he says, "is a real one. Disrespect in one arena can breed disrespect elsewhere". He asks whether a "lifeboat" argument (the choice of lesser evils) can be used in defense of xenotransplantation.

Just as phylogenetic proximity is a measure of potential immune rejection, it also is a measure of how humans value other species. Is killing a primate more serious than killing a pig? Is it about how human-like the species is?

Do humans have the right to use other species for their own (medical) purposes? If so, what are the conditions or limits? Respect for living beings means not treating them as a

means to an end, an object. Immanuel Kant said this applied to humans, but not to the rest of nature. Environmentalists point out that objectification and commodification of their life forms have caused us to create the ecological conditions that imperil our own species–A utilitarian ethic Judges an action by effects on humans, a utilitarian would argue that it is wrong to mistreat animals, because it can make them dangerous, not because mistretment is intrinsically wrong. By this kind of logic, raising pigs for transplant organs might be criticized for its effect of coarsening human sensibilities. This is essentially the old antivivisectionist argument, "Deep ecologists" would say humans are just one of many species, no more intrinsically worthy of respect than any other. Human behavior vis-à-vis other species might make them less worthy of respect. [pc] Another perspective, from Buddhism, is that of "dependent coarising". It holds that there is no independent self or separate existence of species. Humans must treat other beings as they would treat themselves, because existence depends on and is inseparable from the rest of the web of living beings – if there ought to be some reciprocity in our relations with nature, then Xenotransplantation bestows no boon to animals.

Raising animal populations for research and drug production has become more sophisticated since the advent of recombinant DNA technology. Government regulations currently protect laboratory animals, but how will they protect genetically-modified farm cows, created to produce proteins in their milk for research experiments (onco-mouse, knockout mice) or animals to be "harvested" for their cells or organs ? Animals that are used as a source for tissue and cell transplant are regulated as biologicals, under FDA, Regulations on animals in a research setting also apply. The 1996 PHS Guideline suggests that existing regulations should be followed for transplant animals, and that transplant trails should be reviewed by animal care committees as well as institutional review boards (IRBs).

In what way do these uses of animals raise new ethical issues? Is a threshold crossed by raising larger mammals just to supply "spare pans" for humans ? The gift ethic is supported by regulation in the United States. Scandals surrounding human organ procurement argue for the preservation of this ethic — raising animals for their organs as a for-profit enterprise may raise temptations to stretch this ethic. It appears that the breeding and raising of animals for transplant purposes will require extensive monitoring to avoid transmissible diseases as well as genetic or pharmacological alterations to side-step various mechanisms of immune rejection. It is certain that the U.S. Patent and Trademark Office (PTO) will receive more applications in this area, and that the unacceptability of financial ability to pay as a selection criterion, the realistic odds that equal access to xenotransplantation can be achieved, given the potential expenditures that will be necessary, are slim. In 1996, for example, the average annual cost of an allograft organ transplant per individual ranged from $118,845 for a lung transplant to $19,195 for a kidney transplant.

Why is the federal government funding an expensive and risky new technology when it will benefit a few people and when one-third of the U.S. population, mostly women and children, are uninsured and, hence, without any health care? As Tristram Engelhardt puts it. The debates concerning the allocation of treatment resources such as transplantation recur and show no promise of abating. Some controversies have a staying power because they spring from unavoidable moral and conceptual puzzles. One cannot answer the question simply with scientific data, but only by balancing values. Background values of equity, decency, fairness, cost-benefit tradeoffs, individual rights and the limits of state authority must be involved.

If an individual loses "nature's lottery" by incurring a health condition that requires an organ transplant, and the "social lottery" by not having the economic resources to pay for a transplant, can or should a social insurance system redress this misfortune by spending

common resources on transplants? Or should the system spend the resources on universal preventive health care? A sort of "global commons" argument exists; while big ticket technologies carry large opportunity costs out of the public funds available for basic services, administrators may choose to provide the higher ticket services in order to stay competitive with other institutions that provide them, and thus draw more prestige and patients – As in the global commons, each player contributes to the dissipation of the common resource by behavior that is rational to an individual, but not for the common good.

PUBLIC ASSENT

The ethics of human transplants takes a new twist with xenotransplants, in that the latter raises the serious possibility of diseases creating major public health risks: "Xenotransplantation is a unique medical enterprise. It puts the public at risk ... [and] it has to be the public that says, they do not accept that risk, or they accept it". The moral importance of this transaction should not be dismissed lightly just because the donor is an animal.

ALLOCATION OF ORGANS

Never enough organs to meet needs. Much of the raison d'etre for xenotransplantation is based on organ shortages. But even if we accept the xenotransplantation and the technology is successful, allocation issues still have to be worked out fairly, and not simply as an economic commodity. A national structure of organ procurement and allocation, NOTA, establishes priority rules and procedures, A reliable supply of organs could increase U.S. annual expenditures for transplant surgeries, because more people would get them. If costs rise, as might be expected, how will this affect allocation, particularly to less-than-affluent patients? How will access to human organs be affected? What ethical problems arise in allocation?

Justice and fairness require that society's burdens and benefits be borne equally. Democracy requires that the medical professionals, patients, and the body politic have a voice. Physicians should not be forced to choose between saving a life and distributing organs fairly.

DISTRIBUTION OF MEDICAL RESOURCES

Health insurers and health maintenance organizations must weigh the efficacy and costs of alternative treatments. In the case of kidney transplants, the cost of maintaining a patient with renal failure on dialysis for years is less than the cost of transplant surgery, but the net cost in public health care amount is huge in either case. In Oregon, where health care rationing has been developed to allocate public money as equitably as possible, organ transplants are not covered for reimbursement.

LIVING THINGS AS PROPERTY

One effort to raise public awareness of ethical issues in biotechnology was the recent patent application by researcher Stuart Newman and activist Jeremy Rifkin. Claimed are three methods of creating human-animal chimeras. Genetic material is moved from one species and placed into the embryo of another. Even though the inventors have stated that they have no intention of using the patent to produce such chimeras, they fist under possible applications of the techniques the production of organs for transplant into humans. On the surface, this patent does not differ from some patents already issued, such as the "geep" (sheep-goat chimera) or implantation of human "early passage" and embryonic stem cells into the embryos of another species. However, Newman and Rifkin seek to drive a nail into the heart of biotechnology by putting the morality of life patents at issue. As a way to challenge biotechnology patent issues, the tactic is clever. It gives these joint-inventors standing to have an "interfer-

ence proceeding" declared by PTO when any similar patents are filed. They hit their mark, because PTO released a statement within days, declaring that it would not allow patents on part-human inventions, PTO said that these inventions might violate public policy and the morality aspects of the utility requirement. PTO's press release went on to cite an 1817 opinion by Justice Story on the utility requirement, which excludes inventions "injurious to the well being, good policy, or good morals of society". Patent law authority Donald Chisum raised issue with the public policy doctrine, noting that, in fact, a patent approval can be withheld only if the invention has no honest and moral purpose. [ibs] Nonetheless, two days later, PTO Commissioner Bruce Lehman asserted his authority to determine the morality of an invention. He said the press release was necessary to make it clear that "there will be no patents on monsters, at least while I am commissioner".

What is interesting is that PTO policy was issued when it was. Is PTO really shocked by Newman and Rifkin's patent's subject matter? It is quite similar to many patents already issued or in process, Chimeric techniques have been around for several decades. In this case, researchers are attempting to use them to overcome immune barrier problems in xenotransplantation. Moving human cells into donor animals or animal cells into humans has not raised red flags at PTO before–Newman and Rifkin's application is different only in that it calls a pig a pig, so to speak.

Rifkin and Newman's goal is to prevent the commercial exploitation of the technology before it has had a fall public airing of its ethical implications. Rifkin has long been a critic of biotechnology; many industry representatives and academics concede that this move may force a high profile public debate on the issues. It may also buy time for researchers to clarify some of the risks of necessary limits in applying the technology, PTO rejected this patent in June 1999, but an appeal is being prepared.

Even biotechnology industry lawyers concede there is no legal consensus on drawing a line on which life forms can and cannot be patented. In the past, the Thirteenth Amendment to the U.S. Constitution, outlawing slavery, was understood to bar human cell patents. Commencing on issues raised by Newman and Rifkin's application, David Mickei, of the Biotechnology Industry Organization, calls it a "grey area", Researcher David Porteous, of the UK Medical Research.

Council's Human Genetics unit, says, "Setting aside the biological arguments, this is very much a mix of a legal and philosophical discussion. It would certainly be a useful extension of the debate". And Jonathan Marks, professor of biology and anthropology at the University of California/Berkeley says, "If this is what it takes to encourage geneticists to think more about humanitarian issues, I am all for it".

The European Patent Office, on the other hand, is considerably more sensitive to ethical issues. The latest draft of its biotech patent policy specifically excludes as "unpatentable" any inventions whose exploitation or publication would be contrary to public policy or morality. These include: (1) procedures for human cloning; (2) procedures for modifying the germ-line genetic identity of human beings (alterations to genetic materials that are inheritable); (3) changes to the genetic identity of animals that are likely to cause suffering without substantial medical benefit to man or animal, and animals resulting from such processes; (4) methods in which embryos are used; and (5) methods for artificial production of human embryos containing the same genetic information as another human being, dead or alive.

BREAKING NEWS

In May 2000, a stack of internal documents was leaked to Uncaged Campaigns, a British animal rights group. It documented experiments financed by Imutran, a leading xenotransplant

research company, and conducted by Huntigdon Life Sciences in Cambridgeshire, England. The experiments involved transplanting genetically-modified pig organs into monkeys and baboons. These experiments are also being done in U.S. research and medical centers.

The documents covered the log of experiments over several years in the late 1990s. Over 420 monkeys and nearly 50 baboons died in the tests. The average survival time was 13 days, Uncaged published the documents on the Internet along with a summary report on them, "Diaries of Despair", and called on the British government to halt xenotransplantation research and set up an independent Judicial inquiry. Not long after, Uncaged's material was removed from the internet. Imutran, citing breach of confidentiality and copyright violation, got a British court order prohibiting uncaged from further publishing or discussing the documents, Britain's Daily Express newspaper also received copies of the documents and wrote a scathing article in September 2000 reporting that the documents showed days or weeks of animal suffering, incompetence in the conduct of the experiments and for less success with the experiments than was claimed by Imutran. According to the Express, "Imutran has given a highly selective account of its achievements".

Responding to the furor, Imutran said the animals don't suffer and the Daily Express report was misleading. The British court order also forbids any further publication or reporting on the documents by the newspapers.

CCAC GUIDELINES ON TRANSGENIC ANIMALS (1997)

The Canadian Council on Animal Care (CCAC) is responsible for the oversight of animals used in research, teaching and testing. In addition to the *Guide to the Care and Use of Experimental Animals,* Vols. 1 and 2, which lay down general principles for the care and use of the animals, the CCAC also publishes guidelines on issues of current and emerging concerns. The CCAC *guidelines on: transgenic animals* is the second of this series and has been produced by the scientific subcommittee of the CCAC. The creation and use of genetically-modified animals is a rapidly evolving field of research, therefore, these guidelines will be subjected to regular review.

The following guidelines for transgenic animals are provided: to assist Animal Care Committee (ACC) members and investigators in evaluating the ethical and technological aspects of the proposed creation, care and use of transgenic animals; to ensure that transgenic animals are used in accordance with the CCAC statement *Ethics of Animal Investigation*; and to ensure that the well-being of Canadians and the environment are protected.

By definition, the term "transgenic animal" refers to an animal in which there has been a deliberate modification of the genome – the material responsible for inherited characteristics – in contrast to spontaneous mutation (FELASA, September 1992, revised February 1995). Since 1981, when the term "transgenic" was first introduced by J.W. Gordon and F.H. Ruddle, genetically-engineered animals have become increasingly important as research subjects.

Transgenic animals are used: in the basic biological study of regulatory gene elements; in medical research, to identify the functions of specific factors in complex homeostatic systems through over-or under-expression, as models of human disease; in toxicology as responsive test animals; in biotechnology as producers of specific proteins; and in agriculture and aquaculture to improve yields of meat and other animal products. This list is not inclusive; the use of transgenic animals is likely to expand in the future.

There are three main methods used for the production of transgenic animals: DNA microinjection; retrovirus-mediated gene transfer; and embryonic stem (ES) cell-mediated gene transfer.

DNA microinjection is the first method that was developed and provides the underlying concept for the other two methods. The introduced DNA may lead to the over or uder-expression of certain genes or to the expression of novel genes. The integration of the introduced gene into the host DNA, which is accomplished by the microinjection of DNA into the pronucleus of a fertilized ovum, is a random process and the introduced gene will not necessarily insert itself into a site that will permit its expression. Therefore, other methods have been devised, including vector-mediated gene transfer and homologous recombination, to increase the probability of expression. Retro-viruses are commonly used as vectors to transfer genetic material into the cell. The third method uses homologous recombination of DNA to permit precise targeting of DNA sites in embryonic stem cells. If the homologous sequence to be introduced into the cell, carries a mutation or a gene from another species, the new sequence will replace the specific targeted gene. This procedure is the method of choice for gene inactivation, the so-called "knock-out" method and is of particular importance for the study of the genetic control of development processes.

Transgenic animals provide the investigator with an extremely powerful tool for the development of disease models, since the mechanisms of gene regulation will receive a greater understanding. In addition, the use of transgenic mouse models which more closely mimic the human disease can replace the need to use more sentient animals as models. The better specificity of models may in time also lead to a reduction in the number of animals used. Genetic modification of livestock may also be seen as a benefit to human health, in the economic and efficient production of important pharmaceutical proteins.

In parallel with the development of transgenic technology, ethical concerns have arisen about the use of this technology. These concerns are wide ranging and encompass animal welfare, human health and environmental issues. They include animal suffering caused by the expression of transgenes inducing tumors or neurodegenerative diseases, etc., the possible escape of transgenic animals into the environment, not to mention the possibility for the modification of the human genome.

The production and use of transgenic animals are subject to all of the considerations raised by the CCAC *guidelines on: animal use protocol review*. Protocols must, therefore, be reviewed in the same manner. However, a close look must be given to the procedures involved and in particular to possible welfare concerns for the progeny from transgenic animal creation protocols. For these reasons the guidelines also require a *Transgenic Information Sheet* (Appendix) to be completed with the protocol submission.

In implementing these CCAC guidelines, ACCs and investigators considering the welfare of the animals in the proposed study will have to take into account the special features of each transgenic strain. In addition, they will have to be sensitive to ethical concerns and alert to technological changes in this rapidly evolving field. The CCAC anticipates that modifications to the guidelines will be required as this evolution occurs.

1. Investigator and Animal Care Committee Responsibilities

(*a*) *Education*

It is the responsibility of the ACC to ensure that all its members are informed about the ethical and technological aspects of transgenic animal use. A suggested reading list is attached. It is also recommended that researchers applying for ACC approval to create or use transgenic animals be conversant with ethical concerns surrounding the use of these animals, and be prepared to justify their work as being in the public interest.

(*b*) *Proposals to create new transgenic strains*

(*i*) Standard procedures for creating transgenic animals can be dealt with by ACCs according to their usual practices for surgical procedures.

(*ii*) In reviewing applications for creation of novel transgenic animals, ACCs should determine that:

- the investigator has competent technical assistance and experience in the necessary record-keeping for breeding colony maintenance;
- arrangements for surgical procedures, colony housing and maintenance, have been discussed with and approved by the local Animal Facility Management.
- the investigator and the technical staff involved in daily monitoring of the transgenic colony are familiar with signs of distress in the species of study;
- a frequent, reliable, thorough, and documented monitoring system is in place to detect behavioral, anatomical and physiological abnormalities indicative of animal distress; and
- endpoints for survival are clearly defined.

Standard operating procedures (SPOs) can be developed to deal with these concerns.

(*iii*) Proposals to create or use transgenic animals should include information about expected phenotype (as indicated in the Appendix), to include information about anticipated pain or distress levels in the transgenic animal, measures which will be taken to alleviate such distress, and the required monitoring system.

(*iv*) Proposals to create novel transgenic initially should be assigned CCAC category of invasiveness level "D". If approval is merited, it should be provisional, limited to a 12-month period, and subject to the requirement that the investigator report back to the ACC as soon as feasible on the animals' phenotype, noting particularly any evidence of pain or distress.

After receiving the report from the investigator, the ACC may confirm approval of the proposal and adjust the level of invasiveness. However, if the animals are noted to be suffering unanticipated paid or distress, the ACC will ask the investigator to provide a revised protocol which will minimize and alleviate distress, and will reconsider its approval of the proposal.

(*c*) *Proposals to utilize existing transgenic strains*

(*i*) A proposal on transgenic animals may have two parts: creation of the transgenic animals, and subsequent experimental manipulations of the animals. Except where subsequent manipulations are restricted to observation and euthanasia of the transgenic animal, creation and use proposals should be considered as separate proposals.

(*ii*) In reviewing use proposals, ACCs should consider whether procedures regarded as acceptable in non-transgenic animals, are still acceptable in transgenic animals where altered phenotype may impose additional stresses.

(*iii*) Proposals to use existing transgenic strains should also include the information requested in the Appendix.

(*d*) *Accounting*

(*i*) Estimates of all animals to be used or generated in a transgenic study should be stated in proposals to the ACC, listed by use category (*e.g.,* oocyte donors, pseudopregnant females, male "studs", successful transgenics, etc).

(*ii*) When completing the *Animal Use Data Form* for reporting annual animal usage to CCAC, investigators should identify transgenic animals separately from non-transgenic animals in the "Species" column.

(*iii*) To reduce overall animal use, CCAC encourages, when appropriate, assignment of non-transgenic animals, bred in a transgenic creation procedure, to other ACC-approved protocols. Asymptomatic heterozygotes must be clearly identified and should only be used for breeding purposes when the investigator is aware of their altered genotype. Accounting procedures within animal facilities must prevent double-counting of such transferred animals in annual use statistics.

(*e*) *Containment*

(*i*) All proposals for creation or use of transgenic animals must assure the ACC that risks to human health and the environment are minimized to an acceptable level. For transgenic animals created using micro-injection or replication-defective viruses, the containment risks are limited to those associated with the escape of the animal and interbreeding with wild stocks. Proposals should include information about:

- containment and security procedures in animal facilities and, if applicable, during transportation when importing the animal;
- plans for recapture should a breach of containment occur; and
- the consequences to human health or wild populations should containment fail.

(*ii*) For commonly-used transgenic species, each animal facility should have SOPs for containment, which can be referenced by proposals.

(*ii*) ACCs should discuss with the institutional Biohazard Committee any proposal which raises biohazard containment concerns.

(*f*) *Other regulations*

(*i*) ACC approval of a proposal does not relieve the investigator of responsibility to satisfy the regulations of any other governmental agencies. For example, creation of any transgenic fish strain requires approval of the Department of Fisheries and Oceans. Biohazard approval may also be required for some proposals.

2. Responsibilities of CCAC

(*a*) *Education*

To update at least every two years a reading list on ethical and technical aspects of transgenic animal use which can be distributed to members of ACCs, this list to include articles appropriate for all members.

(*b*) *Accounting and reporting*

To include in its annual usage statistics separate totals for transgenic strains of each species used in experiments.

CCAC GUIDELINES ON ANIMAL WELFARE

This section outlines animal welfare concerns which are likely to arise in the creation of transgenic animals and their maintenance in the laboratory setting. Consideration will also have to be given to developments which involve species to be held outside the confines of the laboratory.

1. The CCAC Guidelines on Transgenic Animals

In addition to the *Guide to the Care and Use of Experimental Animals,* the CCAC has recently developed *guidelines on transgenic animals* that will be subject to regular review due to the fast rate of evolution of this field. The intention behind the production of these guidelines is to assist the ACC members and investigators in evaluating the ethics of technological

aspects of the proposed creation care and use of transgenic animals; to ensure that transgenic animals are used in accordance with the CCAC statement *Ethics of Animal Investigation;* and to ensure that the well-being of Canadian and the environment are protected.

2. ACC Protocol Review

The creation and use of transgenic animals are subjected to all of the considerations raised by the CCAC *guidelines on animal use protocol.*

Review: However, special consideration must be given to the procedures involved and in particular to possible welfare concerns for both the parent generation and the progeny.

Evaluation of proposals for the creation of transgenic animals may be divided into two interrelated parts: first, the justification for creation of the particular transgenic animal; and secondly the welfare issues underlying the creation process itself. Special attention must be devoted to new protocols that use, for example, previously uncharacterized vectors or new transgenes, and/or are being performed by investigators who are new to the techniques.

As in all animal experimentation, justification for the use of the transgenic animal involves weighing the possible benefits of the experiment (*e.g.,* advances in biomedical knowledge, the understanding and treatment of disease, improvements in production of foodstuffs or pharmaceuticals) versus the consideration of the ethical cost of the experiment in terms of the potential suffering of the animal. This is particularly difficult for novel transgenic animals as it is not possible to predict with absolute certainty what the effect of a novel transgenic manipulation will be on the animals. For this reason, the protocol must include a strategy to address unanticipated suffering and to establish endpoints for the termination of the experiment. For these reasons, the guidelines require a transgenic information sheet to be completed with the protocol submission. In addition, a separate protocol is required for the creation of a novel transgenic animal, and for its subsequent use.

Category D level of invasiveness must be assigned to each creation protocol, until the effects on the progeny are known. Any harmful effects observed must be reported to the ACC.

The review of transgenic animal use protocols must take into consideration the effects of the transgenic modification on the animal itself, in addition to the subsequent effects incurred by the procedures.

As with any other laboratory animals, transgenic animals must be accorded high standards of care and use. Therefore, all standard operating procedures for laboratory management, human health (investigators and technicians involved with transgenic animals), and animal welfare (as part of the creation protocol, during the subsequent development of the progeny and as part of the animal use protocol) have to be evaluated accordingly.

LABORATORY ANIMAL MANAGEMENT

The implication of transgenic techniques for animal welfare have been discussed by Moore and Mepham (1995). Specific welfare aspects have to be taken into consideration with transgenic animals. They include: the extent of discomfort experienced by the parents during the experimental procedures; the effect of the expression of the transgene (the modified gene inserted) on the created transgenic animal; and the effects on their progeny.

Physical and biological containment for transgenic animals should be adequate to assure the biosafety of the animal care staff which work with the animals, to prevent any possibility of the transfer of the gene within the non-transgenic colonies maintained in the same facilities, and to protect potentially immuno-compromised transgenic animals from pathogens.

The purpose of any breeding operation is to preserve the traits of interest and the restrict causes of genetic variability. Some problems associated with the breeding of transgenic mice may arise. For example, during the creation of transgenic mice, contamination of the media used in collecting eggs and blastocysts for microinjection can occur.

Establishing and maintaining lines requires careful management. As part of the general process of transgenic animal creation, each animal used must be carefully identified. Cage cards and good records with details of breeding information are necessary to be able to identify with certainty the genetic characteristics and modifications of the animal. The data recorded should include the identity, breeding, pedigree and any other pertinent data such as any dates, observations or laboratory analysis information. Since transgenic animals are not easily replaceable, the cost of containment is an important factor in transgenic experimental design.

Embryo freezing is used for the preservation of transgenic strains. To protect colonies against disease, contamination or any other cause of loss, a large number of preimplanted embryos are kept, by cryopreservation. This also reduces the cost of maintaining a transgenic mouse line when it is not needed for experimentation.

With the development of transgenic animals, just a small genomic change can induce unpredictable and quite drastic changes at the level of the whole animal. This is the main challenge for transgenic animal management. It is therefore important to have a clear procedure for monitoring the animals and for dealing with unanticipated suffering.

THE NEED FOR ETHICAL REVIEW

The evaluation of animal and human welfare as it may be affected by biotechnology is a complete issue. One of the elements most notable in this process is the absence of an informed sense of the processes involved. ACCs share the responsibility for educating members on relevant aspects of animal care and use. Education concerning transgenic animal care and use with particular importance, involving the careful consideration of the reasons and manipulating the genome of any organism as genetic engineering is a most competitive social issue.

Bioethical review process is complicated by the fact that many techniques and developments in biotechnology are eligible for patent. The reluctance of biotechnologists to reveal proprietary information is understandable. Current work in fish culture, genetically-altered animals for organ replacement, and cloning underlines the fact that transgenic research is wide ranging. To be able to provide a competent review, ACC members need to develop similar broad understanding of the underlying principles.

A thorough discussion of biotechnology issues, including transgenic animals is needed, particularly to develop some consensus as to the relative value of benefits to be obtained from the use of transgenic animals. One of the more challenging questions is how to account for the interests of the animals involved.

The field of transgenic animal biotechnology is likely to become of increasing importance as the techniques develop further and are applied to many more animal species. Welfare and ethical concerns will also continue to evolve. Consequently, education together with thoughtful ethical decision making will remain the keystone of the review of transgenic protocols.

The CCAC has made a commitment to review the guidelines on transgenic animals on a regular basis.