

**PRIME MINISTER'S SCIENCE, ENGINEERING
AND INNOVATION COUNCIL**

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MOLECULAR MEDICINE

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Terms of Reference:

- What are the emerging research areas / enabling technologies that will revolutionise medicine?
- Explain the science of the Human Genome Project, and Therapeutic Stem Cells.
- Provide examples of therapeutic applications from these areas.
- Discuss commercialisation of relevant applications.
- Flag the public policy (ethics) issues that are under consideration.

CONTENT

EXECUTIVE SUMMARY.....	3
INTRODUCTION.....	6
GENERATING IDEAS.....	6
The Science of the Human Genome	6
The Science of Stem Cells	8
Impact on Clinical Medicine	10
The Future	13
ACTING ON IDEAS.....	14
Molecular Medicine in the Australian Economy	14
Australian Molecular Medicine in the Global Market	16
CREATING AN IDEAS CULTURE.....	18
Molecular Medicine in the Community	18
Ensuring Effective Regulation	20
THE WAY FORWARD - To Health and Wealth.....	22
APPENDICES.....	25
1 Ethics and Safety of Research in Humans	25
2 Approaches to Gene Testing	26
3 Use of Stem Cells in Medicine	28
4 List of Australian Molecular Medicine Firms	29
5 Some Examples of Federal Government Support	30
6 Some Key Overseas Molecular Medicine Firms	31
7 Working Group Members	32
8 Glossary	33
OVERVIEW OF PRESENTATION.....	35

EXECUTIVE SUMMARY

The Third Great Technology Revolution

We are in the early phases of one of the most important periods of discovery in human history – the exploration of the genetic basis of life and its diversity, called *Genomics*.

The differences between individuals, and between limes and lemons, are embedded in genetic programming, with environmental factors sometimes affecting the expression of this ‘software’.

Those who exploit this genetic information will dominate the biological industries of this century, industries, which will account for half of the world’s economy. Entirely new industries and opportunities, which cannot yet be guessed, will be created.

Genomics is now widely regarded as the third great technology revolution, after the Industrial Revolution and Information Technology.

Genomics and advanced molecular and cellular biology are attracting considerable public and private investment in other countries.

The first stage of the *Human Genome Project* has been completed, consisting of the sequence of over 3 billion chemical bases in human DNA. This was an international effort, this milestone being announced by both US President Clinton and UK Prime Minister Blair. Besides humans, the DNA sequences or genomes of many other species, such as infectious bacteria and viruses, have been completed.

Genes

The DNA sequence of bases provides a template to identify and analyse genes and their functions. Each gene is a blueprint that encodes one or more proteins. Proteins are the basis of cells, tissues, and organs, underlying human growth, development and physiology.

The next major challenge is identifying what all the genes code for, and involves matching genomic sequence data with other biological data. The use of computers is emerging as a feature of this area, as vast amounts of information must be assembled and analysed. Computational biology helps develop and refine various models of biological systems.

In the broadest sense, the intersection of genomics knowledge, gene manipulation, and cell manipulation, with optics, biomaterials, and information technologies is creating new vistas. It is driving the development of innovative new industries, as happened with the Internet in the information revolution. As with any innovation, the right mix of discovery, ideas, technologies, venture capital and creative well-trained people is required.

Medical Breakthroughs

Medicine will benefit from new pharmaceuticals, vaccines, antibiotics, diagnostics, and the ability to predict accurately clinical outcomes. For the first time in history, gene therapy holds promise for the treatment of genetic disorders. New approaches involving gene therapy

will also treat viral diseases and cancer. Gene therapy clinical trials are underway in this country.

At the cellular level, the application of stem cell therapies to treat burns, heart disease, liver disease, neuromuscular disease, neurodegenerative diseases and other conditions associated with ageing will advance the prospects for recovery from disease and injury.

Ethical issues will be raised by these technologies. The Australian regulatory framework to handle such issues is well regarded locally and overseas. New advances, such as re-programming of our own cells, and the development of universal stem cell lines compatible with transplantation may help address some of the ethical issues that are currently encountered.

Impact and Outcomes on the Patient, Doctor, and National Budget

The practice of medicine will allow more effective preventative strategies. There will be much more personalised medicine, i.e., drug doses, where risk calculations can be based on an individual's genetic makeup, rather than population statistics.

This will result in a net positive impact on health economics through reduced hospitalisation and the capacity for more focussed public health care expenditure. As well as treating or curing diseases, the development of genomics will produce a very positive impact on the quality of the lives of many individuals.

Issues and Challenges for the Future

The Human Genome Project's future impact on medicine provides an opportunity for Australia to join the formative stages of a new scientific and technological revolution that will create new industries, new jobs, and wealth for Australia.

Australia is presently one of the ten or so leading countries in the world in biomedical research. A failure to convert this into a strong position in the new world of advanced medicine will cost dearly in terms of lost opportunities, sliding competitiveness and further pressure on a negative balance of trade position.

The race is on, but Australia's scientific base is declining. Australia is the only leading country in medical research not investing heavily in genomics, bioinformatics and cell technologies. Australia has just over \$4 million allocated for genomics projects in the year 2000. Canada has a \$160 million investment in large-scale genomics projects, and Singapore is investing \$1 billion of government funds for genomic and life sciences.

Australia must compensate by being as strategic and focussed as possible. Countries lacking our traditional strengths are doing just that and are rapidly going past us. Ireland has recently focussed on IT and biotechnology. Singapore is now emerging as the likely capital for biotechnology in the Asia-Pacific region.

There is an urgent need for public and private investment in molecular medicine. Public investment is needed for the capture of the primary strategic platforms, and private investment is needed to convert the knowledge and rapidly growing technology base into new industries.

Equally important is the need to reverse the brain drain. We need to attract and retain key personnel with research and business excellence, on the basis that we are serious about being

a player in molecular medicine. We cannot continue to allow our best scientists to be headhunted for two to four times Australian research salaries by Singapore, Europe, and the USA.

We need leadership and courage. We need to engage in strategic planning that enables us to be competitive in molecular medicine, and delivers the best economic and health outcomes for the entire Australian community.

A VISION FOR MOLECULAR MEDICINE

In the general research and innovation policy environment:

- the recent increase in biomedical research funds is very welcome and provides a strong platform for R&D initiatives;
- the reports *Chance to Change* and *Unlocking the Future* are a benchmark to adopt;
- industry R&D support measures need to be enhanced.

In molecular medicine research and innovation:

- new support for education in cross-disciplinary areas such as bioinformatics and bioengineering is required;
- internationally competitive research fellowships to enhance the commercial productivity of Australian molecular medicine should be established;
- courses in intellectual property management for graduate students should be promoted;
- the existing regulatory frameworks and bodies must be continued, ensuring they have the support and resources to deal with increasing complexities;
- cost-recovery models used by regulatory bodies must be reviewed when research is coming from publicly funded institutions;
- inducements for relevant firms to relocate regional and head offices and production facilities to Australia are critical.

The Australian Government needs to respond rapidly and with confidence to the genomics and cell biology revolution, joining scientists and institutions at the vanguard in delivering to the Australian community improved medicine, increased jobs and economic growth.

INTRODUCTION

This paper is about the new sciences of genomics and stem cell therapies. Its title, 'molecular medicine' captures the application of these areas for the HEALTH and WEALTH of Australians. The promise of powerful disease prevention advice to individuals, and therapeutic treatment with few side effects, and the wealth generated from selling such services overseas, is substantial.

To achieve the goals of health and wealth for Australia, the framework for human molecular medicine development needs strengthening. Deep, systemic infrastructure must be built in areas such as bioinformatics. Critical mass in areas like cell culture, manipulation, storage and material exchange is necessary. The regulatory framework must be maintained, but at the same time responsive to changes which may occur. The public interest, and anxiety, arising from the potential application of new knowledge from developments in genomics and cloning is obvious in the high level of relevant press coverage. Mechanisms are in place to involve the public in debating these issues. More proactive education-based programs will go a long way to reducing public ignorance of these complex technologies.

There is a range of Australian molecular medicine companies at different stages of early development. Now that tax rules have been adjusted for investments in such companies, the tax regime is much better for encouraging major investments in these areas by big US investment houses and superannuation funds.

This paper considers the issues associated with molecular medicine within the three key themes of the Chief Scientist's discussion paper *The Chance to Change*, and the Miles Report *Innovation - Unlocking the Future*: ideas, commercialisation, and culture.

GENERATING IDEAS

The Science of the Human Genome

The Genome

The genetic code of a human being can be read on the Internet now. It's not exactly light reading, from start to finish it's nothing but the letters A, T, C and G repeated over and over in varying order, long enough to fill more than 200 telephone books. The sequence of DNA, otherwise called the 'genome', is a best seller for the world's biologists in understanding nature, and businesses interested in health and wealth. It is reading our own instruction book - how we walk, talk, think and sleep.

The human DNA sequence is the information superhighway of all human life. The prestigious American journal *Science* described this area as the third great technology revolution, after the industrial and information technology revolutions¹.

The identification of the sequence in the human genome of its 3 billion letters, through the joint efforts of the *Human Genome Project* and the US firm *Celera Genomics*, is the flagship

¹ US semiconductor giant Motorola has declared that biotechnology will be its next major investment. This is the third major investment area for Motorola, following radio in the 1920s and semiconductors in the 1950s.

for a fleet of projects exploring the genetic basis of life and genetic diversity. Many different genome projects are proceeding in parallel. These include human pathogens (live disease causing agents) such as viruses, bacteria, fungi, parasites and worms, as well as model species like fruit flies and mice. One of the most surprising results of the project has been the discovery of just how similar many things are at the genetic level, and paradoxically, how diverse life really is.

OUR HUMAN ROOTS

The pattern of DNA in living people has answered some of the big questions about our earliest origins. The genome is a history book showing that the entire 6 billion member human species traces back 7,000 generations to a tiny founding population of some 60,000 people.

The pattern shows that the species emerged in Africa about 200,000 years ago and first left the continent to begin its worldwide spread 100,000 years ago.

Our species has only a modest amount of genetic variation - the DNA of any two humans is 99.9% identical. One group of 55 chimps in West Africa showed more genetic diversity than the whole of humanity.

The Human Genome Project has identified genes (specific segments of the DNA sequence) coding for the production of exquisitely precise proteins that carry out the numerous functions needed to maintain cells and keep them alive. Up to 100,000 genes may exist in the human genome to make these various proteins. However, these genes occupy only about 2 per cent of the genome, while the other 98 per cent is termed 'junk' (perhaps evolutionary leftovers) in the sense that it does not contain coding genes. A proportion of this 'junk' DNA has been effectively used for identification purposes, eg forensic applications.

The next step, understanding the shape of the many proteins produced by these genes, and how they work in health and disease, will revolutionise medicine.

These proteins are the precision cellular machines and structural components used, for example, to build the human cell, form other types of structural building blocks, convert food to energy, carry oxygen around the body, and detoxify drugs. Databases now contain some details of when and in which tissues of the body various genes are turned on, the shapes of the proteins the genes code for, how the proteins interact with one another and the role of all this in specific diseases.

The four approaches now emerging to exploit the new genome sequence are defined below. The first two will vastly improve drug design (as demonstrated by Biota's flu drug). The last two will deliver to individuals specific advice on genetic disease control.

- *Proteomics* looks at proteins produced in cells and how they interact.
- *Structural genomics* looks at the shape and structure of individual proteins².
- *Bioinformatics* uses computers to predict, from a one-dimensional protein sequence (like a string with letters threaded through it), how a protein folds into a specific shape in three dimensions.

² Protein structure studies of these types require deep infrastructure. Major national research facilities such as supercomputers or x-ray crystallographic analysers can help here. In the past, it took years to determine the three-dimensional structure of a protein crystal. New techniques using a Synchrotron, with powerful X-rays, can reduce the time to weeks. There are about 80 synchrotrons operating or planned in the world. Australia is the only major trading nation without one.

- *Functional genomics* involves looking for changes in DNA sequences (mutations) in inbred experimental animals, such as laboratory mice, to identify the function of genes.

The current situation is akin to having access to a huge library of knowledge but being illiterate. It is a start on the long journey to understand the function of genes, to therapeutically manipulate these genes, and to understand their interaction with the environment.

The sequence of the genome provides vast amounts of information that lends itself naturally to computation. This area of research is largely evolving into an information science, with computational biology and bioinformatics assuming central importance.

Computer based, holistic models of life will be developed in the near future and with increasing accuracy and reliability as the century unfolds. The expression *in silico* is used now to refer to biological computation and modelling of living processes and organisms in contrast with the well known biological term *in vivo* for tests and modelling in living things.

Computer modelling will be four tiered: the genes in DNA code for the busy and precise proteins; these proteins form into metabolic, signal transduction and regulatory pathways; these in turn transform into cells; which then transform into tissues and whole organisms.

The human genome sequence constitutes part of the first tier. At this stage there is agreement that the number of genes in the human genome is somewhere between 40,000 and 100,000. Identifying all these genes and their variations, and understanding their functions is a great global scientific effort.

In summary, it is the view of the Working Group that genomics, proteomics, bioinformatics, and stem cell research, discussed next, are emerging as the among most important areas of biological science for the early part of this century.

CELERA GENOMICS DATABASES

A coup for Australia is that it is among the first in the world to secure the right to access five of Celera's databases and use their advanced tools for analysis. This is the result of a three-year pre-paid national subscription to Celera's databases, negotiated and paid for by the NHMRC. This has involved an up front payment by the NHMRC. In addition, principal investigators from Australian publicly funded institutions will pay an annual licence fee for access to these databases.

The Science of Stem Cells

One possible way of delivering healthy genes to diseased tissue is by use of stem cells.

Throughout life, all tissues have to be maintained in proper working order. Routine maintenance is performed either by maintaining a single set of cells in a healthy state for life (as in the nervous system), or by replacing cells as they die with new cells (as in the blood, the gut, and the liver). Tissues able to replace cells as they die contain special cells, termed *stem cells*.

Stem cells are unspecialised cells that give rise to differentiated cells. In other words, they retain the ability to differentiate into any of the 200 to 300 specialised cells and tissues of the

human body. The general hallmark of stem cells is their balance between maintaining their own numbers and spawning progeny that go on to become specialised tissues.

Stem cells are used routinely in clinical medicine. For example, the blood cell system of cancer patients is often damaged or destroyed as part of chemotherapy. The damaged blood cells can be replaced by transplanting blood stem cells that have been collected from the bone marrow or peripheral blood of donors, or even from patients themselves. In this way the bone marrow can be replaced or repaired by the transplanted stem cells.

In terms of genetic disorders, the severe form of beta thalassaemia can be cured or converted to a less severe disorder by stem cell transplantation with cells obtained from newborn cord blood.

Stem cells offer medicine ways to construct human tissues and organs such as the heart, avoiding a self induced immune reaction against the introduced replacement organs.

This type of molecular medicine is called 'cellular therapy', and can be thought of as bioengineering. It involves the manipulation of DNA within cells, in particular, undifferentiated stem cells, to construct the new tissue.

Some stem cells are immortal in the sense that they can be grown in the laboratory indefinitely, i.e., in cell culture. Various culture conditions can be used to trigger differentiation and thus the type of cell that grows. As illustrated earlier, stem cells have been isolated from bone marrow and newborn cord blood. Recent experimental data suggest that adult differentiated cells might be induced to change into other cell types. A newly established source of stem cells is embryonic stem cells.

EMBRYONIC STEM CELLS AND CELL THERAPY

A new type of stem cell has been discovered in human fertilised eggs a few days old - the embryonic stem cell. These cells are special because, unlike stem cells from adult tissues, which are present in very low numbers, they can be grown in unlimited quantities. Many people consider these cells have the potential to revolutionise many aspects of clinical medicine. There are ethical, legal and social considerations in respect of the use of embryonic stem cells that are currently being addressed, locally and internationally.

These cell lines are immortal and will grow unlimited numbers of cells in the laboratory. Their maintenance and differentiation into specific cell and tissue types can be controlled; discovery of the 'factors' involved will identify potentially new and important regenerative medicines. The cells also have the potential to be valuable targets for new drug discovery and toxicology.

Two research groups have produced embryonic stem cells, one in the USA and the other in Australia. Research in Australia has shown these stem cells can develop into each and every type of tissue of the human body (multipotential) and can be directed, for example, into forming pure neuronal precursor cells (nerve stem cells). Adult stem cells, on the other hand, are a little difficult to identify, isolate and multiply, and with a few exceptions, remain elusive and of limited use in medicine to date.

Some believe that embryonic stem cells may be produced without the need of a whole egg cell line in the future by identifying and synthesising the relevant egg cell proteins, which are required.

THERAPEUTIC CLONING

Therapeutic cell cloning of the future is illustrated by the following procedure:

Cells taken from your skin are grown in culture in the laboratory and single cells then introduced into an egg cell voided of its own DNA. Within a week, cells can be harvested. These contain personalised embryonic stem cells.

The modified stem cells are then cultured in the laboratory under conditions, which induce them to differentiate and grow into a particular tissue. These cells, placed in the person from whom the skin cells were taken, are less likely to be rejected by the immune system since they carry an identical genome to the host. Using this technique, many of the problems of organs for transplants might be overcome. Many damaged organs only need repair, and stem cells provide a potential source. Patients suffering from certain degenerative diseases of the brain, liver, pancreas, blood, as well as burn victims, could benefit.

HUMAN CLONING (REPRODUCTIVE CLONING)

The possible production of cloned persons using nuclear transfer technology (similar to the well-publicised Dolly experiment) has no medical merit and serves no beneficial purpose in contemporary society. Reproductive cloning is strongly opposed by medical and scientific professional bodies and societies as unethical. Australia's health ministers have recently agreed to develop legislation to ban human cloning in all states and territories. Embryos formed by nuclear transfer in the conduct of therapeutic cloning must be confined to the laboratory and regulations created to ensure they are never transferred to the female reproductive tract. The House of Representatives Standing Committee on Legal and Constitutional Affairs is conducting an *Inquiry into scientific, ethical and regulatory aspects of human cloning*, likely to report in early 2001.

Impact on Clinical Medicine

The impact on clinical medicine will be in the three following areas:

(1) Genetic Testing.

Science is showing that genetically based diseases mostly arise from complex interactions between many genes in our DNA and environmental factors. However, we have the capability of identifying significant marker genes that can assist to predict a person's risk for cancer, or other diseases. Should a person choose to undergo these genetic tests, the resultant profile could be helpful to them in evaluating their lifestyle choices.

Genetic testing for these marker genes and for other variations in germline (inheritable) DNA sequences predictive of significant health effects is already well established here and overseas.

In the near future it will be possible to undertake thousands of genetic tests simultaneously to provide rapid diagnoses and predictions on disease susceptibilities. These new 'microarray' technologies (sometimes called 'chips') will lead to radical changes in pathology testing and the availability of genetic tests. Approaches to testing are outlined in appendix 2.

GENES AND THE ENVIRONMENT

Genetics tends to be oversimplified by people saying we have a “gene for cancer” or a “gene for diabetes”. In some cases this is correct, eg there is one gene which causes cystic fibrosis. On the other hand, for many complex disorders, genes determine only so much. Identical twins have identical genomes, yet one may develop juvenile diabetes and the other typically does not. Understanding the role of genes should help pinpoint environmental factors and teach us how to avoid potentially harmful interactions between the environment and our genetic makeup. These types of genetic disorders are called multifactorial, ie genes and the environment are interacting.

(2) *New Drugs.*

Analysing the genome of human pathogens will allow powerful new antibiotics and vaccines to be developed. Analysing the human genome will also yield information on how new drugs can be identified and lead to novel approaches to therapy.

Antibiotics revolutionised medicine after penicillin was discovered, but their potency in recent years has declined. Bacteria that are resistant to drugs have now become an increasing problem in hospitals throughout the world. No new antibiotics have been developed for more than two decades. The genes in pathogenic bacteria are new drug targets, weak points in a bacterium's armour. New antibiotics exploiting these weak points are currently in late stage clinical trials. Besides developing new antibiotics, challenges remain in developing drugs for complex and common human diseases such as Alzheimer's disease, diabetes and obesity. With obesity, for example, a hormone called *leptin* helps regulate body weight. *Leptin* is now in clinical trial to determine its efficacy in treating obesity.

SAVING COSTS BY MULTIVALENT VACCINATION

Cost savings from these new technologies can be significant. Recently, NSW experienced problems with rising levels of pertussis in children, because many were not being vaccinated.

Multivalent vaccines where one shot vaccinates against a range of infectious diseases are being developed, thanks to the modern genetic technologies and the targets the genome data provide. Savings will arise from more efficient vaccination programs, far less cumbersome to run and more complete in their coverage.

DRUG THERAPY IS NOT WITHOUT RISK: PRESCRIBING THE RIGHT MEDICINE FOR THE RIGHT PATIENT

In 1994 in the United States, over 2.2 million patients were hospitalised with serious drug related side effects, with about 100,000 deaths. Adverse drug reactions ranked as the 5th leading cause of death in the US in 1994. Knowledge of genetic susceptibility to adverse drug reactions, by testing genes involved in drug breakdown, will provide important future advice for patients.

Pharmacogenetics will provide patients and health professionals with accurate advice on how a particular drug will respond to particular individuals, or whether their genetic make up suggests other forms of treatment may be better. It aims to provide ‘the right medicine for the right patient’.

Drugs termed tricyclics are used to treat depression. These drugs are removed from the body by breaking them down in the liver. The rate they are broken down depends on a liver protein called cytochrome P450. Around 10 per cent of Australians break the drug down slowly, while 1 per cent do it extremely quickly, and the rest are somewhere in between. Genetic testing for the cytochrome P450 gene shows which of these classes a patient falls into. Treatment can then be tailored to avoid severe side effects or a lack of efficacy in tricyclics use. This would be a more sophisticated and accurate way of determining drug dosage than present approaches which rely on an average dose, or weight / height considerations.

(3) *Gene therapy.*

Another mechanism by which the Human Genome Project will begin to revolutionise medicine is through gene therapy. Gene therapy involves the insertion of DNA or genes into the cells of the patient. Traditionally, gene therapy was considered a means by which to cure rare genetic disorders. Today, gene therapy is being used as a potential alternative source of treatment in a wide range of conditions, including HIV, cancer and genetic disorders. It will be several years before gene therapy becomes widely available to the community. Gene therapy applications are only in the trial stage throughout the western world. In Australia we are still in a position to be actively involved in the development phases, ensuring that in the longer term we reap the rewards.

Gene therapy is directed at replacing genes in so called somatic cells, i.e., all cells in the body except the sperm and egg. Germline gene therapy (where inheritable genes are affected), in which the genes are put into eggs or sperm, is not permitted in Australia and in most western countries because of ethical concerns that in manipulating the inheritable genetic makeup of an individual, harm may be done to future generations.

Examples of gene therapy approaches are expanding. Immunodeficiencies that lead to severe, often lethal infection during childhood are already being treated by gene therapy. Gene therapy may be useful for multisystemic diseases like cystic fibrosis. Promisingly, cancer cells have had extra genes inserted into them to try and make them conspicuous and easily destroyed by the immune system. Gene therapy trials are also underway to promote growth of blood vessels in heart disease patients. Cancer and HIV gene therapy seem to be the main focus of industry at present.

HAEMOPHILIA

Gene therapy potentially offers an alternate treatment for haemophilia sufferers, treatment for whom now places an enormous strain on blood supply availability.

Haemophilia is a hereditary blood defect almost exclusively of males.

To treat the condition at the present time, the factor promoting clot formation is isolated from healthy blood donations, and given to sufferers to alleviate life-threatening situations. Gene therapy by insertion in sufferers of the gene coding for the clotting factor will be a major benefit to patients and the community by lessening the need for fresh blood.

Many barriers to effective gene therapy remain, such as getting DNA into enough of the correct cells to be effective (eg into stem cells responsible for life-long tissue generation), and ensuring that the replacement gene functions properly for many years rather than a few days or weeks. However, it is almost certain that over the next decade gene therapy will deliver remarkable changes to clinical practice.

ETHICS

Ethical principles apply to all aspects of health care, medical research and the medical genomics revolution.

The experimental, development and commercialisation phases of human medical genomics must be governed by the application of nationally agreed ethical guidelines to safeguard the interests of research subjects.

Australia has in place such national guidelines. These offer a highly valued and respected system for overseeing the ethics and safety of research in humans. They establish a climate of ethical expectation for researchers, research institutions and commercial partners.

We must be aware that some ethical issues related to the molecular medicine revolution will be complex. Therefore, our processes and mechanisms for overseeing the ethical and social aspects of this work must be diligently maintained, reviewed and updated as required. The role of the NHMRC and the current regulatory framework is described in appendix 1.

The Future

In the future we can expect scientific advances and applications from two comparative approaches - comparing genomes across human populations, and comparing the human and animal genomes.

Molecular genetic scanning of humans will identify genes and proteins involved in inherited diseases, as well as those that play a role in more common conditions and traits. Genetic test profiles of individuals will show them the degree of their susceptibility to various diseases. Diseases will include cancers, heart disease, stroke, asthma, anxiety, obesity, or hypertension. It may even prove possible to eradicate some of these diseases, thus avoiding their social and financial costs.

Analysis will extend to genetic understanding of complex human traits such as personality and behaviour.

Comparing the genomes of mammals will provide insight into the basis of other complex traits, such as intelligence, development and aging. The chimpanzee and human genomes (which are 99 per cent identical) should help us pinpoint key features, which underlie the rise of higher order thought, consciousness, abstraction, language and music.

In tissue engineering we may be able to replace diseased organs such as a cancerous liver with a new bioengineered liver.

Australia's scientific infrastructure must keep up in these areas. While medical research funding has been boosted through the NHMRC, it is imperative that expertise in cross-disciplinary areas, such as biophysics, x-ray crystallography, philosophy, and many other areas be strengthened. The initiatives proposed in *The Chance to Change* are highly relevant here.

These developments are proceeding at a rapid pace and raise a wide range of ethical issues and philosophical challenges. Some of these will be anticipated, others not. It is also complicated by the interaction of social, economic, cultural and ideological perspectives, which are themselves evolving far less rapidly. Whatever the future of this next scientific voyage, it is certain this century will see enormous changes brought about by medical science.

BIOINFORMATICS - THE FUTURE

Reports on bioinformatics to the US National Institutes of Health (NIH) and to Australia's NHMRC show:

- an urgent need for integration of mathematics and information science into biomedicine, and for computational-based approaches to biomedical research;
- a serious lack of expertise in these areas amongst biomedical researchers; and
- that incentives and funding are needed to stimulate the meeting of these traditionally very different research cultures.

The NIH report notes:

“Researchers now spend less time in their ‘wet labs’ gathering data, and more time on computation. They find themselves working in teams to harness the new technologies. A broad segment of the biomedical research community perceives a shortfall of suitably educated people competent to support those teams. What is needed is a higher level of competence in mathematics and computer science among biologists themselves.

The benefits from the fusion of biomedicine with maths/information science are substantial. A commercial presence is developing that supplements publicly funded institutions, such as the European Bioinformatics Institute near Cambridge. Many major research universities in the US are investing heavily in multidisciplinary centres. Examples include Harvard's Centre for Genomics and Proteomics, and Princeton's Institute for Genomic Analysis”.

Australia has been slow to respond and no major focus of expertise is yet established here. The situation is changing—new bioinformatics centres are forming in Melbourne and Brisbane with funding from State and Federal Governments. A distributed national model for bioinformation science is emerging, based around a network of collaborating nodes in Brisbane, Canberra, Melbourne and Sydney: the Australian National Genome Information Service (ANGIS), centred in Sydney, was established in 1991.

ACTING ON IDEAS**Molecular Medicine in the Australian Economy**

A vibrant Australian industry based on molecular medicine will help transform Australia into the ‘new economy’. This is one industry with the highest promise of successful development because our medical research base is world class and well-established across medical disciplines.

However, it is also one emerging industry that requires both ‘big’ science and ‘big’ capital. Capital and science fuel the growth of the growing molecular medicine industry, as they have done in the past for the pharmaceutical industries of many nations.

To bring a new drug to market costs about \$500 million. Testing requirements and regulatory barriers are substantial. The discovery and commercialisation of new molecular medicines is expensive, time consuming, and high risk.

The early design, and clinical trials, of a new drug involve the efforts of many scientists in a cooperative venture. The large Australian team that developed Biota's influenza drug formed a critical mass of researchers sharing a common goal. This is one aspect of big science. Big science also means access to large-scale research facilities, or ‘deep infrastructure’.

Yet the benefit to the economy can be fundamental, with spin-off benefits from growing support industries, employees earning high wages, foreign exchange earnings, and tax

revenue. The costs of development may be amply repaid to those countries, businesses, and investors that successfully participate in this market.

Success for Australia in molecular medicine depends on the Government facilitating an appropriate innovation framework. This provides a playing field where the rules of the game are clear and equitable, and which is highly competitive in the global economy. The initiatives proposed in the *Miles Report (Unlocking the Future)* are essential to achieve this framework.

Since the knowledge of worldwide molecular medicine inventions is eminently transportable, the health of Australians will be improved whether the inventions and commercialisation opportunities emerge in Australia or elsewhere. However, if Australia becomes merely an absorber of overseas molecular medicine technology, it will forego great economic opportunity. To transfer and absorb knowledge from overseas, we still need to build expertise here, otherwise we will be largely at the mercy of expensive overseas advice that may not be given in our best national interest.

The development of a molecular medicine industry in Australia will provide a wide range of economic benefits, such as Australian start-ups that may grow into transnational firms, and it will also provide social benefits in inspiring the young to assume and manage risks and acquire education in new economy areas.

How will Australian molecular medicine research take its discoveries into the clinic? If companies obtain international patent protection, offer their products to an educated market, and work in a well considered regulatory environment, then new diagnostics and therapies will be widely disseminated.

Australia continues to develop sophisticated clinical trial capabilities. Enhancing Australia's role in the conduct of clinical trials will provide leverage in obtaining the latest worldwide gene technologies from overseas partners.

DEVELOPING A MEDICAL GENOMICS INDUSTRY

Successful development of a profitable medical genomics industry requires:

- a highly trained workforce. In addition to experts in the rapidly evolving fields of stem cell technologies and genetics, we need informed business people. People who understand and can assess emerging technology, patent attorneys familiar with the patent laws in other markets, ethicists and interested parties debating issues;
- maximum financial opportunity and encouragement given to the scientist and business entrepreneurs who are likely to have the greatest chance of success;
- promotion of entrepreneurs as role models; and
- concentration of efforts of government and business in the areas that are most likely to bring rewards. Since the benefits of most technologies are difficult to predict, both curiosity driven and directed research in these chosen areas should be encouraged.

Although the costs to attract high calibre intellectual skills can be large, the costs to acquire equipment is often relatively far less. New companies can spring up overnight, seeded by the ideas of entrepreneurs and money from venture capital funds, existing corporations or government grants.

It will be essential that Government policy aims to have the Australian community invest in these goals and capture the broad economic benefits. This should be achievable through an appropriate tax regime for investors, and regulatory mechanisms for developers.

THE TAX REGIME AND ENTREPRENEURS

Venture capital is the lifeblood of research commercialisation. Although as a percentage of GDP Australian venture capital levels are growing, as shown in the *Miles Report*, we lag far behind the leading provider - Canada. We provide only about 20 per cent the level that Canada provides. For early stage capital the picture is worse, at only 7 per cent Canada's level.

Some might argue that before 1985 no capital gains tax existed in Australia, yet commercialisation of medical research lagged other countries. However, this was in a highly protectionist era for industry which tended not to need to be too outward looking, and perhaps not prepared to take the risk of developing new economy enterprises.

The lesson is that Australia should be internationally competitive in its corporate tax regime to attract foreign investment. Until recently, the tax rules have not been very favourable for high technology risk taking investors. Recent tax changes have improved the environment. While there is still room to relax legislation further, it may be more important to encourage development of entrepreneurs, and development of others skilled in technology assessment.

The states are now more formidable in biotechnology (e.g., Victoria's 'Bio21' and Queensland's 'Institute of Molecular Bioscience' initiatives). Coordination of state and federal activities is essential and highly promising.

Australian Molecular Medicine in the Global Market

Molecular medicine, long in gestation, is internationally recognised by governments and businesses as being one of the most important technological juggernauts of all time. Is this juggernaut likely to run out of steam any time soon?

That would seem unlikely. The amount of information that remains to be discovered in human, animal and plant genomics will take decades to unfold, while the discovery and application of human proteomic information will most likely be continuing at a rapid pace 100 years from now. The non-reproductive use of stem cells is at the earliest developmental stage of all, offering opportunities that will continue to be identified and applied for many decades.

The molecular medicine market is global. Although at one extreme medical genomics will bring personalised medicine that is optimised for geographically and racially identified segments of the population, the technology itself will know no borders. Profits, patent-protected royalties and commercialisation opportunities will benefit the head offices and headquarter countries of the companies that spend money and initiative up front to establish their competitive advantage.

THALASSAEMIA

Examples of past genetic testing might be illustrative. Genetic testing has proved very effective for populations such as the Greek Cypriots in London, who have one of the highest known frequencies of beta-thalassemia in the world and many had chosen not to have children if one parent had the gene. Prospective parents were terrified of having a child with this severe blood disease. A well-organised and culturally acceptable testing program was introduced, and within ten years the population's birthrate had returned to normal.

A similar successful outcome was achieved in the Jewish population in New York for Tay-Sachs disease, a serious neurodegenerative disorder where affected children die in infancy. The benefits of genetic testing can be delivered sensitively to affected populations, and testing offers opportunities to firms across borders.

The medical genomics revolution is inherently knowledge based. Australia can compete successfully despite its distance from many of the world's major markets. The challenge facing Australia is to be maximally efficient as this global race unfolds.

Ernst and Young have suggested that by 2010 there will be 3 million people in North America and Europe involved in a biotechnology industry worth hundreds of billions of dollars.

At the beginning of the 21st century, Australia has the benefit that compared to the US and some European countries the costs of doing pure and applied research are lower in Australia. At the same time, the talent pool and the core educational standards are as great as anywhere else in the world. This gives Australia an economic advantage that we should continue to exploit.

An ever-present risk inherent in a global technology is that the cream of Australia's researchers will be attracted to other countries, drawn by the huge levels of private and government funding in those countries.

SINGAPORE AND MOLECULAR MEDICINE

Some of Australia's top medical researchers - such as the 1996 Nobel Prize winner Peter Doherty - are attracted to overseas opportunities.

Singapore may emerge as a future brain drain for Australia. In June 2000, the Singapore Government announced a US\$1 billion program in life sciences. The first flagship is the Singapore Genomics program. This will receive

US\$ 36 million over its first five years. It will establish a tissue repository / clinical database, genomics, proteomics functional biology and bioinformatics sub-programs. The program places special emphasis on recruiting talented researchers. Salaries are linked to the US dollar and are 2-3 times Australia's levels.

AMGEN

Amgen is an American company that has grown through Australian medical research discoveries. In the 1950s in Melbourne a class of blood factors called Colony Stimulating Factors were discovered.

Amgen markets several products only. One of its principal products is NEUPOGEN®, a colony-stimulating factor used to prevent infection in cancer patients undergoing chemotherapy and bone marrow transplants. Amgen's current market capitalisation is US\$65 billion on the NASDAQ.

To keep our researchers and talented people here or to attract them back armed with their international experience, salaries, funds and career opportunities have to be commensurate with the value that this new sector of the economy has for Australia's future development. One of the most fruitful pathways for molecular medicine development is to attract talented

scientists into exciting jobs. In a global market, Government could catalyse this through new industry post-doctoral fellowships, funded to provide internationally competitive salaries.

In addition, Australia should take every opportunity to host international academic conferences in the disciplines upon which it chooses to concentrate its resources. These conferences could serve a function a little like that for the Olympics, but perhaps be even more important for the national interest. These conferences will bring prestige and attention that will contribute to the fertile discussion of ideas in the Australian scientific and business communities. This may make the Australian research environment more attractive to scientists and maximise the chances that internationally competitive new biotechnologies originate in Australia.

CREATING AN IDEAS CULTURE

Molecular Medicine in the Community

Education is crucial in this area.

The importance of education is well illustrated by the recent reports on human cloning such as the Australian Health Ethics Committee's *Scientific, Ethical, and Regulatory Considerations Relevant to the Cloning of Human Beings*, and the Australian Academy of Science's *On Human Cloning*.

ON HUMAN CLONING

The Australian Academy of Science initiated community consultation on human cloning to ensure wide public debate on the issues raised by cloning of the sheep known as Dolly, and the therapeutic applications of human stem cells.

This involved ethicists, the clergy, scientists, lawyers, and the lay public. There was enormous public interest in the issues. The principal conclusions of the Academy of Science were:

- that reproductive cloning to produce human fetuses is unethical and unsafe and should be prohibited; and
- that human cells, whether derived from cloning techniques, from embryonic stem cells, or from primordial germ cells should not be precluded from use in approved research activities in cellular and developmental biology.

In addition, the Council of the Academy made recommendations that the Minister for Health and Aged Care encourage informed community discussion of cloning techniques; that Australia capitalise on its undoubted strength in medical research by not inhibiting appropriate research on human therapeutic cloning; and that a two tier approval process be adopted for research involving human embryos and embryonic stem cell lines.

Similar interest in the issues associated with molecular medicine is expected.

If benefits from molecular medicine are to be captured for health and wealth creation, a process for addressing concerns about relevant technologies should be in place. Open discussion of ethical questions and confidence in the regulatory framework provides a core part of this assessment. Education of the public and community at large forms another vital component of this process.

Any change in public attitudes to scientific innovation can be slow as evidenced by Justice Kirby's remark³:

"The lesson seems to be that notions of human dignity and what is acceptable, or not, change in time. In part, the changes come about:

- with increasing **public familiarity** with the scientific and technological development;
- with a **perception of the benefits** which they can bring; and
- with a realisation that the **dangers** to human dignity and freedom **may be less than first feared.**"

Although there are strong views held on matters seen to relate to human dignity, much of the public response to the Australian Academy of Science's position statement *On Human Cloning*⁴ was positive. Enabling regulation and moral pressure can be helpful to scientific progress. In some cases, scientists may be able to choose between alternative avenues for experimentation.

What fundamental human values are being touched in a new way by this technology? To avoid polarisation in the community, it is vital that the public information process be thorough and impartial. The community must ask of these new technologies: Who owns it? For what purpose is it to be used?, and Who benefits? The Government can play an important role in leading public discussion to ensure that this is so for Australia. Even given this prescription, the development of public awareness and acceptance will be slow.

Many of these issues are not new. Relevant issues are covered in the following NHMRC publications and are briefly detailed in appendix 1:

- *National Statement on Ethical Conduct in Research Involving Humans*;
- *Guidelines for Genetic Registers and Associated Genetic Material*;
- *Ethical Aspects of Human Genetic Testing: an Information Paper*.
- *Guidelines for Ethical Review of Research Proposals for Human Somatic Cell Gene Therapy and Related Therapies*

Ethical issues which broadly impact on molecular medicine are identified in the box.

ETHICAL CONSIDERATIONS
Social significance and consequences of genetic research
Professional confidentiality and privacy issues
Interpretation of genetic information
Screening
Ownership of genetic data
Access to and release of personal genetic information
Genetic discrimination
Employment and insurance
Prenatal and preimplantation diagnosis
Genetic manipulation

Australia has an excellent international reputation for sound handling of sensitive issues, such as human clinical trials and animal experimentation. Ultimately, this is helping to overcome problems and ensure sound health outcomes in the Australian population.

³ The Honourable Justice Michael Kirby AC, CMG in his speech *The Ten Rules of Valencia*, to the World Health Organisation, January 1999.

⁴ *On Human Cloning, A Position Statement*, Australian Academy of Science, 4 February 1999.

EDUCATION, ETHICS AND LAW

A number of key centres carry out research and education related to the impacts of molecular medicine and include:

- *The Cooperative Research Centre for Discovery of Genes and Common Human Diseases* has adopted a public education role in this area. The Centre engages audiences from various sectors of the community and provides them with scientific knowledge to facilitate informed debate.
- *The Centre of Applied Philosophy and Public Ethics* involves philosophers and ethicists at Charles Sturt University and the University of Melbourne.
- *The Centre of Law and Genetics* involves the universities of Melbourne and Tasmania. Interests include new societal structures for managing research and developments in human genetics in useful and democratic ways.

Ensuring Effective Regulation

What regulatory barriers and incentives exist for the diffusion of novel genomics and cloning technologies?

Patents have been granted for segments of human DNA that are indicative of disease, and exclusively licensed to a limited number of clinical laboratories. This limitation on access to genomics (and cloning technologies) that are indispensable to future research in human molecular medicine and that have been brought about through restrictive licensing arrangements has been raised by the OECD as an issue of concern.

Who will own and control the products available from the new stem cell technologies? Should we entertain the notion of the potential to 'patent life'?

Issues such as these raise important questions for the future of genetic testing services, the diffusion of technology, and the need for coherent international policies.

Worldwide, much of the innovative molecular medicine research is now being done in industry, although it is underpinned by large public investment. Industry protects its inventions and technologies through the intellectual property system, in turn licensing these to users. One example is Celera Genomics, which has carried out much of the human genome sequencing. Australia's NHMRC has entered into a favourable financial agreement with Celera for our researchers to access all of its databases and search tools as necessary.

Scientists in universities and public research institutions, in ways similar to those of many industrial scientists, are expected to capture the intellectual property that is generated from their research. Scientists have for some considerable time been patenting genes and genetic engineering technologies. Australian society invests in research partly because we want to understand our world, and improve the human condition, but also because we want to drive economic growth.

At the heart of investment in new technology development, and the risks this carries for the investor, is the reward available through monopoly grants to inventions provided by the

Australian patent system. A dilemma faced by any patent system is the granting of patents in genomics.

However, the Australian patent system is currently well suited to regulate the commercialisation of molecular medicine. It is compatible with the patent systems of the United States, Canada, the United Kingdom and European countries.

THE AUSTRALIAN PATENT SYSTEM AND GENES

The Australian system provides for patents on biological inventions, including micro-organisms such as bacteria, fungi and viruses; DNA, genes and chromosomes; synthetic genes or DNA sequences and the DNA coding for a gene; plants; and non-human animals.

DNA or genes in the human body are not patentable but “a DNA or gene sequence which has been separated from the human body and manufactured synthetically for reintroduction into the human body for therapeutic purposes is patentable”.

“Products of such living patented matter, eg food supplements, drugs and processes for synthesising the material or making the products” are also patentable. So are other applications of patentable inventions – probes for a particular gene; higher plants/animals carrying the gene; and methods for using a gene or genetic technology. “Human beings, and the biological processes for their generation” are not patentable as they are specifically excluded under s 18(2) of the Patents Act 1900.

Although the patent system itself is effective, researchers and institutions must be educated on how to move from obtaining a patent to launching their product onto the market. Information on advice and the steps to research commercialisation should be more widely made available through the Internet (eg via AusIndustry). Research institutes and universities should be encouraged to collaborate with industry and with each other to advise researchers on how to commercialise their research after a patent is granted. Note that recommendations in *Chance to Change* and *Unlocking the Future* cover these issues.

REGULATORY COSTS

It is proposed that The *Office of the Gene Technology Regulator* will operate on a full cost-recovery basis but these charges are daunting for investigators without commercial backing, and may prevent or delay the development of inventions in Australia after a patent has been granted. Waiving the costs levied by these regulatory bodies for research undertaken in not for profit institutions would help overcome this problem. Irrespective of whether the Office charges fees (an issue yet to be decided by Government), it is likely that research institutions will incur significant costs in complying with the new system. The new system will replace the *Genetic Manipulation Advisory Committee* system of voluntary compliance with guidelines, a system that has served Australian research well for the last 25 years.

Community education about the genomic and biotechnology revolution is vital. Those in the community who are critical or concerned about technology call for new laws to regulate it. In the rapidly emerging molecular medicine areas discussed in this paper, it is not necessary to rush into new legislation, nor to establish new regulatory bodies. There is much existing legislation that can effectively cover the field, and existing regulatory bodies can still remain effective in these circumstances. Guidelines which have been very effectively promulgated in the past to cover a range of potentially contentious issues remain relevant within the context of the molecular medicine revolution.

There is a long tradition of NHMRC guidelines establishing codes for conduct of research and medical practice. There are financial and legal sanctions for non-compliance. The most recent *National Statement on Ethical Conduct in Research Involving Humans* (1999) clearly defines statutory considerations binding on institutions and industry whether or not they are

funded by the NHMRC. Key documents such as this have been endorsed by other national bodies (AVCC, ARC, AAS etc) ensuring compliance is as wide as possible. Since the NHMRC guidelines are evidence of accepted standards and reasonable care for the purpose of the law of contract and negligence, non-compliance can have legal consequences.

Community education projects can emphasise potential benefits of genetic technology and also the regulatory machinery that *already exists* to prevent abuse. For example:

- *health insurers* are prohibited from discriminating on health grounds in issuing policies; all premiums are set at the same rate regardless of risk.
- *life, superannuation and disability insurers* are allowed to base their premiums on risk but must be able to justify discrimination on actuarial or statistical data.
- *employers* are prohibited from discriminating on the ground of disability in deciding who should be employed, or the terms of employment; and when employment contracts are terminated, subject to the duty to provide a safe workplace under occupational health and safety legislation.
- *service providers* are prohibited from discriminating on the ground of disability in the provision of services unless providing the service would impose unjustifiable hardship on the provider.

THE WAY FORWARD - To Health and Wealth

Australia needs to step up research that creates new intellectual property for use as the enabling technology of the new economy. There are unique opportunities that presently languish because the gearing up of basic development is too slow and the vibrant interface with investment is largely absent. Australia should:

- invest in early stage, clever ideas in molecular and cellular genomics that can be converted to intellectual property of significance for commercialisation. The investment profile should be at least of the order of potentially competing countries, e.g. Singapore;
- establish a vibrant interface between the early stage research and start-up ventures. The entrepreneurial scientist-business individuals that are challenged by new ventures that unite research and investment are largely missing from the Australian biotechnology landscape. They need to be attracted by remuneration packages that include performance options for establishing internationally competitive spin-offs from basic research;
- encourage multinational drug and biotechnology companies to establish permanent regional offices in Australia. Their absence is a handicap for the establishment of joint ventures and R&D syndication of valuable intellectual property;
- undertake intelligent and diligent analysis of trends in global change, including the appearance and disappearance of corporations as mergers and takeovers alter investment directions;
- be a global leader in carefully chosen areas of molecular medicine. Utilisation of new research by strategic alliances and mergers with financial institutions and companies that

have compatible intellectual property and rights is extremely important because this can be a weakness in the grade-up for economic return;

- respond rapidly to opportunity, a major limitation presently. This requires financial backing of patent application fees, the rapid linkage of intellectual property with investors and upgrade of the research and development phase to convert the initial intellectual property to commercial product, sales and returns. Currently the public and private sectors operate too slowly and the opportunity is dissipated or lost to others;
- provide new funding for early stage start-ups modelled on the US's small business program. The infrastructure available in Biotechnology Australia, NHMRC and ARC should be used to rapidly evaluate applications for support; and
- invest in large-scale infrastructure such as a synchrotron, high-resolution magnetic resonance imaging facilities, high speed computing facilities and buildings to allow co-location of research groups and industry.

Specific areas in molecular medicine which are in particular need of attention include:

- **Bioinformatics:** the rapid changes in this discipline are easily appreciated when one considers the effect that the Internet is already having on the lives of ordinary Australians. The nation's expertise in bioinformatics must be rapidly expanded, and talented individuals with bioinformatics skills must be kept in Australia. This will involve a range of departments, both state and commonwealth, starting in our schools and universities.
- **Education:** in terms of the molecular revolution and the role that it will increasingly play in the health of Australians, education strategies require considerable foresight and investment. The education of our future research leaders, as well as the current health professionals, requires coordination and must be started now. For example, with the completion of the Human Genome Project, the number of human genes identified will increase exponentially. Will we test or undertake research for all these disorders, or should some form of priority be established based on national needs and expertise?
- **Regulation and ethical practice:** Australians are generally comfortable with the regulations and standards of ethical practice practised in medical research and the clinical workplace. Existing structures must recognise rapid changes and have adequate resources to respond. However, we should not remain complacent but ensure that the increasing complexities inherent in the DNA technologies do not stifle productive research, and allow ethically sound studies and clinical trials to be conducted. The community must be fully aware of new developments, and be an active participant in all major decision making. The trend towards full cost recovery in government-provided services is laudatory. On the other hand, public-good research must not be penalised by regulatory constraints which can only be overcome by service fees. The current debate centred on the proposed Gene Technology Bill and how it will be funded, is a contemporary issue in this respect.
- **Genetic testing:** The growing number of tests for both rare and common disorders is placing greater demand on medical practitioners to order these tests. This will place increasing pressure on healthcare professionals skilled in medical genetics or genetic

counselling. All health care professionals, including medical practitioners, will need advice and guidance. How can the Colleges/Professional Associations be facilitated to advance these skills? Do we want to undertake predictive DNA testing for all potential diseases? A better model for both the resourcing for DNA testing, and determining priorities is required. This model should not be constrained by state boundaries and must be rapidly responsive to changes occurring in genetics. At present, DNA testing is an ad hoc arrangement which is inefficient and cost ineffective.

- Genetic and cell therapies: These offer novel strategies by which the important public health issues of our time – cancer, heart disease, infectious diseases, dementia and other effects of ageing – will be tackled in the future. Australians have been very innovative in these areas. Defining what Australians are best at, and ensuring that strategic goals can be reached, are priorities for this country.

WORKING TOGETHER

While the Australian community's richness lies in the diversity of its cultures and interests, when it comes to genetics, all members of the community share a common interest: their genes. Genetics is everybody's business. Our leaders and the community need to work fast and effectively to ensure that the benefits of the genetics revolution are captured to enhance the health and wealth of all Australians.

APPENDICES

1 Ethics and Safety of Research in Humans

Ethical considerations are as germane to good research as are scientific principles. Ethical guidelines have the objective of defining standards of behaviour to which researchers should adhere. Guidelines established by the NHMRC for research involving humans have as their primary purpose the protection of the welfare and rights of participants in research. The ethical and legal responsibilities which researchers have towards participants in research reflect basic ethical values of integrity, respect for persons, beneficence and justice. The responsibilities, issues, and features of ethical review set out below accord with accepted moral and scientific principles defined in international declarations, conventions and guidelines from organisations such as UNESCO and the UN, and listed in *National Statement on Ethical Conduct in Research Involving Humans* (NHMRC, 1999).

Ethical Review in Australia

Australia ratified the Declaration of Helsinki in 1964 and in 1966 the NHMRC issued its first *Statement on Human Experimentation* which closely adhered in the principles of the Declaration of Helsinki. In July 1999, after 4 years of extensive public consultation, the NHMRC issued a revised *National Statement on Ethical Conduct in Research Involving Humans*. Its purpose is to protect the welfare and rights of participants in research and to facilitate research of benefit to humankind.

All Australian universities and other institutions in receipt of research grants from the NHMRC or ARC are obliged now to establish Human Research Ethics Committees (HREC), constituted and operating in accordance with the *National Statement on Ethical Conduct in Research involving Humans*. The *National Statement* guides the composition of HRECs, ensuring broad community, ethical, legal and professional oversight. Compliance by HRECs is monitored by the Australian Health Ethics Committee (AHEC) a principal committee of the NHMRC. The composition of AHEC, which also contains community, ethical, legal and professional members, is spelt out in the NHMRC Act 1992.

The Scope of the ‘*National Statement on Ethical Conduct in Research Involving Humans*’

The *National Statement* is generic and adequately covers all the immediately foreseeable ethical issues which may arise from the medical genomics revolution. In its introduction, it outlines the principles of ethical conduct. It provides detailed directions regarding the composition and functions of HRECs. It has an additional 16 sections providing guidance in such subjects as genetic research, the use of tissue, clinical trials, multi centre trials, innovative therapy, privacy and intellectual property. It has been endorsed by the Australian Vice-Chancellors’ Committee, Australian Research Council, Australian Academy of Humanities, Australian Academy of Science, and the Academy of Social Sciences in Australia. It applies to all disciplines of research impacting on or involving humans.

Additional Ethical Guidance and Research Regulation Processes

The NHMRC through AHEC and its other principal committees issues discussion papers and formal guidelines from time to time, which address ethical issues of concern to the

community. Early in 2000, AHEC issued three separate papers on aspects of gene testing (see 'Molecular Medicine in the Community', page 17). The NHMRC is presently preparing a paper on xenotransplantation. Gene therapy research proposals must be approved by the NHMRC's Gene and Related Therapies Research Advisory Panel before being considered by HRECs. The proposed Office of the Gene Technology Regulator is also very relevant to this regulatory review process.

Changing Perspectives on Ethical Principles

The *National Statement* emphasises four guiding principles for the ethical conduct of research in humans: integrity, respect for persons, beneficence and justice. In the last two decades, respect for persons, as reflected in such issues as fully informed consent and a careful weighing of risk versus benefit has been a dominant guiding principle. This will not be displaced, but it is anticipated that attention will focus in the coming decade on the principle of justice. This will encompass such matters as equity of access to research studies and new therapies. It ought to provide guidance as well in the distribution of new services, and take into consideration social consequences such as employment, and the development of new local industries

Emerging Pressures on the Ethical Review System, and on the Safety of Research – Lessons for Australia

The risks of unethical research include potent harm to individual participants and also to public support for all human research. The Australian ethical review system is extensive (there are over 200 HRECs registered with AHEC) and generally highly valued and respected. It is based on honorary contributions of trusted members of the community who devote much time to a very responsible task. Four members of each committee must be external to the institution.

Similar systems in other western countries have been challenged in recent times by researchers who have failed to adhere to approved research protocols. For adequate ongoing protection of the Australian community (including protection of economic opportunities offered by the medical genomics revolution) it is crucial that all participants in research and development in this sphere understand and acknowledge the need for a robust process for independent ethical review of research protocols.

2 Approaches to Gene Testing

- **Population screening** involves the testing, after informed consent of individuals, including newborns, irrespective of their family history of a disease, for the presence of genes that predispose them to certain diseases.

Example: Test for the presence of genes which act together to increase the chance an individual may develop diseases like diabetes. This enables at risk individuals to make lifestyle decisions (eg about diet, exercise, regular monitoring) that reduces their risk of disease development.

- **Predictive testing** at the request of an individual shows if a disease-causing gene is present and the individual is at high risk of developing a disease. Usually there is a

family history and the underlying genetic alteration (mutation) is known. For some conditions, such as Huntington's disease, all carriers will develop the condition. For others, such as Alzheimer's disease, the risk is increased but not 100 per cent.

Example: Several genes known to predispose people to certain cancers have been identified (eg. the genes predisposing to genetic forms of breast cancer, and the genes which predispose to certain types of colon cancer). If the genetic alteration causing cancer in a family is known, then family members can determine if they also carry this alteration or not. Those with the mutation require more intensive long-term follow up or specific treatment to try and prevent the cancer from forming. Those without the mutation can be reassured that their risks are reduced (although they still remain at risk for the more common or sporadic forms of breast and colon cancer).

- **Carrier identification** is used to determine whether a person carries a copy of a recessive disease gene. This is useful since children born to parents who are both carriers of a recessive disease gene will have a 25 per cent chance of being affected by the disease.

Example: Carrier identification includes genetic tests used by couples whose families have a history of recessive genetic disorders and who are considering having children. Three common tests include those for cystic fibrosis, Tay-Sachs disease, and thalassaemia.

- **Diagnostic testing** is used to confirm a clinically suspected diagnosis of a disease in a symptomatic individual.

Example: An individual may have symptoms suggestive of a particular condition, but invasive procedures are required to confirm the diagnosis. In the case of haemochromatosis (a condition caused by excessive iron in the body), a liver biopsy is the definitive way in which to make the diagnosis. However, a liver biopsy is associated with complications including death. Therefore, a faster and less dangerous way to confirm haemochromatosis which is suspected in an individual is by a DNA gene test.

- **Prenatal diagnosis** is used to diagnose a genetic disease in a developing fetus using techniques such as chorionic villus sampling or amniocentesis.

Example: The types of prenatal genetic tests performed include screens for chromosomal abnormalities that become more common as the age of the mother increases, and tests for specific genetic abnormalities the parents are known to carry.

3 Use of Stem Cells in Medicine.

Stem cell research will impact on several areas, including:

- **Discovery of Hormones and Factors.** Factors that maintain, multiply and direct stem cell differentiation are likely to be extremely valuable therapeutics in their own right.

Example: Colony stimulating factors in blood, discovered in Melbourne many years ago, act on blood stem cells and are now used in millions of patients worldwide to protect against the side effects of chemotherapy and to mobilise stem cells into the blood, providing a cheaper and less painful alternative to bone marrow transplantation.

- **Drug Discovery.** Stem cells can be used for assessing the action of new drugs, drug toxicology, and can replace animal testing.

Example: Drug discovery relies on the capacity to test potential new drugs in the laboratory and on animals before they enter clinical trials. This testing determines whether there are toxic effects. Because stem cells can generate many different tissues, they may offer a more thorough and economic means of testing drug toxicity.

- **Tissue Regeneration and Bioengineering.** Stem cell technology may regenerate tissues in severe pathologies and injuries. This is likely to be one of the most exciting developments in medicine in the next decade. Tissue regeneration is being coupled to materials science to produce a new field of tissue bioengineering.

Example: Much excitement is being generated by the possibility of using neuronal stem cells and their derivatives to promote recovery from degenerative diseases such as Parkinson's Disease, Alzheimer's Disease, Multiple Sclerosis, and damage caused by stroke or spinal injuries. Bioengineering projects include constructing nerve bundles, primitive organs, and reconstructive surgery.

- **Gene Therapy.** Stem cells can have the desired gene or genes inserted into them and are induced to produce the tissue required for transplantation. This corrects the genetic disorder.

Example: This approach may be important for new immunisation strategies against infections such as HIV and malaria.

4 List of Australian Molecular Medicine Firms

Firm	Abbreviated Function, Market Capitalisation
Medical genomics:	
PsyGene Pty Ltd	A pharmacogenomics business undertaking research oriented to mental illness and dementia.
Bionomics Limited	Strategy is to identify genes affected by epilepsy and breast cancer and validate them as potential drug targets by the analysis of DNA from large, multi-generational family groups, positional cloning of the genes, and DNA microarray techniques. <i>Capitalisation AU\$ 27m.</i>
The Australian Medical Research & Development Corporation (AMRAD)	AMRAD consists of 11 Australian research institutions as members. One advanced product is a gene coding for a growth factor for new cardiac blood vessels. It is called human vascular endothelial growth factor B. <i>Capitalisation AU\$ 107m.</i>
eBioinformatics Inc	Offers access via the Internet to analysis tools and genomic and protein databases. Manages a supercomputer.
Bionomics	The discovery of genes associated with epilepsy and breast cancer. <i>Capitalisation AU\$ 27m.</i>
ExGenix Operations	Locate genetic lesions of common human diseases. www.exgenix.com.au
Autogen	Research portfolio includes a 'Metabolic Diseases Gene Discovery Program'. This includes the Israeli Sand Rat Genetics Project for Obesity and Diabetes; Robotic Microarray Technology for Gene Discovery; and a Human Genetics Project for Obesity and Diabetes. <i>Capitalisation AU\$ 47m.</i> www.autogenlimited.com.au
Virax Holdings	Virax is currently focussed on a clinical trial of a vaccine produced by gene technology. The vaccine's use is pending regulatory and ethics committee approvals. A clinical trial is on early-stage HIV-infected patients. <i>Capitalisation AU\$ 30m.</i> www.virax.com.au
Metabolic Pharmaceuticals	Therapies for metabolic diseases such as obesity and type 2 diabetes. The company adopts a "virtual" structure, minimising infrastructure and overhead costs while maximising access to world-class expertise. <i>Capitalisation AU\$ 24m.</i> www.metabolic.com.au
Proteome Systems Limited.	Proteomics. Includes development of scientific instrumentation, bioinformatics analysis, and research towards drugs against human disease. Spin-off from Macquarie Uni. www.proteomesystems.com
Cellular Therapies:	
Stem Cell Sciences Ltd	A web site describing this company is under construction and will be available at www.StemCellSciences.com.au
ES Cells International (ESI)	Australian-Singapore commercial investment firm drawing Australian and global interests together in a discovery program based on human embryonic stem cells and their directed differentiation for potential gene and cell therapy. Supports research in Australia, Singapore, Israel, The Netherlands and USA on human embryonic stem cells.

FuCell Pty Ltd	FuCell concentrates on the creation of human hybridomas, which produce human monoclonal antibodies. The objective of one line of research is to adapt existing FuCell technology to create unique hybrid cell lines of commercial interest through the insertion of DNA material into existing cell lines.
Bresagen	Stem cell research; gene technologies. Product pipeline includes biotherapeutics for myeloid leukemia, breast cancer, allergic disease and organ disease. Acquiring CytoGenesis Incorporated (a US firm) to advance Bresagen's cell program. <i>Capitalisation AU\$ 44m.</i>
<i>Instrumentation:</i>	
Axon Instruments	Axon Instruments designs and manufactures high-performance instruments and software for genomics, proteomics, and drug screening. A scanner provides high-resolution microarray imaging for gene and protein expression studies. Bioinformatics software organises, analyzes and manages data from the scanners. High throughput screening robots in development will be used to test protein-drug interactions. <i>Capitalisation AU\$ 569m. www.axon.com</i>

- The above is not meant to be a complete list. A complete online list of Australian biotechnology companies is available at www.biotech.isr.gov.au
- In **Australian Biotechnology Report 1999**, Ernst & Young and the Department of Industry, Science & Resources estimated the number of Australian core biotechnology companies as 120. 82% are not listed on the Australian Stock Exchange and are still predominantly at the early stage of growth and development. About 40% are spin-offs from research institutions.
- Many molecular medicine firms are identified and discussed in the book "**Biomedical, Biotechnology and Pharmaceutical Innovation - Australia's Opportunities**", first published in 2000 by CL Creations Pty Ltd and the Health Media Group. The Advisory Board for this book was chaired by Professor John Shine.
- The only billion dollar biotechnology firms in Australia are **CSL** (AU\$ 5 b.) and **Cochlear** (AU\$ 1.4b.), both originating in public research activities. Axon Instruments, which is involved in genomics, is the next largest with a capitalisation of over half a billion Australian dollars.

5 Examples of Federal Government Support, through Programs

Program	Example
NHMRC	<i>Program in Medical Genomics</i> , \$4.2m in 2000-2001, planned to rise to \$10m pa. This will fund 5-8 projects a year, ranging from sequencing of pathogens to high-throughput genetic epidemiology.
CRC program	<i>CRC for Discovery of Genes for Common Human Diseases</i> . Core partners are Exgenix, Univ. of Qld., QIMR, and WEHI. Total program funds are \$13.1m, and total Centre resources are \$40.6m, for 7 years life.
R&D Start	Bresagen was the recipient in September 2000 of a \$4m grant to research Parkinson's disease and bone marrow disorders. Proteome Systems Ltd is the recipient of a \$3.3m grant to develop instruments for proteomics research.

- Programs that support biotechnology in Australia are outlined comprehensively in **Australian Biotechnology - progress and achievements**, available from Biotechnology Australia (c/- Department of Industry, Science & Resources) {*Biotechnology Australia* is an initiative of the Federal Government, with \$30m over 5 years.}
- Biotechnology R&D expenditure in the public sector is estimated at \$257m for 1999. This is about 6% of total public R&D. Biotechnology R&D expenditure by businesses is estimated at \$234m for 1999. This is about 5% of total business R&D.
- Two State Governments, Queensland and Victoria, are investing heavily in support for biotechnology.

6 Some Key Overseas Molecular Medicine Firms

US Firms (publicly listed)	Comments, Capitalisation (early November)
Celera Genomics	Genome databases. <i>Capitalisation US\$ 4.5 billion</i>
Human Genome Sciences	Patents on 7500 human genes. <i>Capitalisation US\$ 10.8 billion</i>
Incyte Genomics	Genome databases. <i>Capitalisation US\$ 2.5 billion</i>
Millennium Pharmaceuticals	Pharmacogenomics. <i>Capitalisation US\$ 15..8 billion</i>
Ciphergen Biosystems	Instruments and chips for proteins. <i>Capitalisation US\$ 1 billion</i>
CuraGen	New drug targets via proteomics. <i>Capitalisation US\$ 2.3 billion</i>
Myriad Genetics	Selling genetic tests. <i>Capitalisation US\$ 2.6 billion</i>
Affymetrix	Selling gene chips and gene scanners. <i>Capitalisation US\$ 4.4 billion.</i>
Large Scale Biology	Proteomics technologies. <i>Capitalisation US\$ 0.4 billion</i>
European Firms	
Oxford GlycoSciences (UK)	Proteomics for new therapeutics.
Oxford Molecular Group	Drug discovery software. www.oxmol.co.uk
Geneva Bioinformatics (Switzerland)	Proteomics databases and software tools. www.genebio.com
Lion Bioscience (Germany)	Bioinformatics. Alliance with Bayer. www.lionbioscience.com
Compugen (Israel)	Specialised bioinformatics tools for data mining. www.cgen.com
New Zealand Firms	
Genesis R&D Corporation	Builds databases as genomic platform for discovery of novel genes with commercial value.

7 Working Group Members

Professor Nicholas Saunders - a physician, and Dean of the Faculty of Medicine at Monash University, a position he took up in 1998. Previously, he was Dean of the School of Medicine at Flinders University in Adelaide and prior to that was Professor of Medicine at Newcastle University. Currently, he is Chair of the National Health and Medical Research Council, Chair of the Committee of Deans of Australian Medical Schools, and an *ex officio* member of the Prime Minister's Science, Engineering and Innovation Council.

Professor Sue Serjeantson - Visiting Fellow at the Australian National University and science policy consultant. She is President of the Federation of Australian Scientific and Technological Societies (FASTS) and an *ex officio* member of the Prime Minister's Science, Engineering and Innovation Council. From 1994-97 Sue was Director of the Institute of Advanced Studies and Deputy Vice-Chancellor, ANU. Her research in human molecular genetics and in improving the outcome of organ transplantation has been recognised this year by the Order of Australia award.

Dr Alan Finkel - Chief Executive Officer of Axon Instruments, Inc., a California corporation listed on the Australian Stock Exchange. Dr Finkel founded Axon and is primarily involved now in product development and strategy. Axon is the leading world manufacturer of amplifiers and data acquisition systems used for cellular neuroscience research. It is a leading international supplier of fluorescent scanners and image processing software for DNA and protein microarrays. Axon develops bioinformatics software for the analysis of genomic expression.

Dr Doug Hilton - Director of the Cooperative Research Centre for Cellular Growth Factors and with colleagues founded the genetics company, Murigen Pty Ltd and the biotechnology consulting company, Quintessential Science. Dr Hilton is a Principal Research Fellow of the NH&MRC and maintains a laboratory at Walter and Eliza Hall Institute which is focussed on understanding how cells in the body communicate with one another.

Professor John Mattick - Professor of Molecular Biology and Co-Director of the University of Queensland's *Institute of Molecular Bioscience* which will be the largest of its kind in Australia when fully established. Professor Mattick is Director of the Australian Genome Research Facility. He serves on numerous Boards and Committees such as the *NHMRC's Research Committee* and the *Australian Health Ethics Committee*. Research interests include molecular genetics, gene expression and genome sequencing.

Professor Loane Skene - Professor of Law at The University of Melbourne and a Barrister and Solicitor of the Supreme Court of Victoria. She has authored two books and published numerous chapters in books and articles in Australian and overseas legal, medical and scientific journals. She chairs the *Australian Institute of Health Law and Ethics*. Professor Skene serves on many committees including the National Health and Medical Research Council's *Gene Therapy and Related Technologies Research Advisory Panel* and *Genetic Registers Committee*; and the Victorian Anti-Cancer Council's *Co-operative Oncology Group* and *Genetics Ethics Committee*. She was also the legal member of the federal *Genetic Manipulation Advisory Committee* for five years (1994-9).

Professor Ron Trent - Heads the Department of Molecular & Clinical Genetics, Royal Prince Alfred Hospital, and is Professor of Molecular Genetics at the University of Sydney. His involvement in molecular medicine comes as a physician and laboratory director involved in DNA testing. His book "Molecular Medicine" won a UK prize for best medical textbook in 1994. He is a member of the NHMRC's *Research Committee*, and has chaired the NHMRC's *Gene and related Technologies Research Advisory Panel* since 1996.

Professor Alan Trounson - Professor of Obstetrics & Gynaecology/Paediatrics and Director of a major research program at Monash University that includes the development and production of multipotent stem cells for gene discovery, functional genomics, cell therapy and tissue bioengineering. One of the pioneers of human IVF and embryo genetic diagnosis and retains interest in human infertility and the genes involved in early human development.

Professor John W White - Professor of Physical and Theoretical Chemistry in the Research School of Chemistry at the Australian National University. He is a Fellow of the Royal Society. He is Science Policy Secretary of the Australian Academy of Science. He led the working groups and public discussion forums related to the Academy's study of human cloning and therapeutic cloning from 1998 to 2000. He delivered the "Commencement Lecture" at St Mark's National Theological Centre on this subject in 1999 and is President of ISCAST, a national Christian organisation studying the science/faith interface.

8 Glossary

Molecular Medicine. For the purposes of this paper this is defined as the application of genomics knowledge and stem cell sciences to human medicine

Genes. These are segments of the DNA sequence that code for unique proteins. Each gene has a unique sequence of hundreds of bases (from adenine A, cytosine C, guanine G, and thymine T).

Proteins. These carry out various bodily functions such as the construction of tissues, chemical reactions (enzymes), or act as messengers (hormones).

Genetic information. This includes both DNA sequence information and inferences that can be made from knowledge of the sequence.

Cystic fibrosis. A serious inherited disorder affecting the lungs and digestive system of babies, children and young adults.

Diagnostic test. A test performed to make a diagnosis of a specific disorder in a person who already has symptoms.

DNA (deoxyribonucleic acid). A linear sequence of bases which encodes genetic information.

Gene. The fundamental unit of heredity consisting of a sequence of DNA, occupying a specific position on the DNA sequence. Each gene encodes the information needed to produce a protein with a specific function.

Genome. The total genetic complement, ie complete DNA sequence. The term can be used with reference to a cell, an organism , or a species.

Germ-line DNA. The DNA passed on by an individual's reproductive cells to children. Somatic DNA exists in cells other than reproductive ones and cannot be passed to children.

Haemochromatosis. Inherited disorder with progressive accumulation of iron in the tissues.

Haemophilia. Inherited disorder of blood clotting resulting from mutations in the factor 8 and factor 9 genes. Results in bleeding into joints and bruising after minor injury. About one in 10,000 boys are affected.

Huntington disease. A progressive inherited degenerative disorder of the brain which begins in mid-adult life and results in an involuntary movement called chorea. Results from mutations in the IT15 gene and affects about 1 in 10,000 people.

Tay-Sachs disease. Inherited degenerative disorder of the nervous system resulting from mutations in the hexosaminidase A gene on chromosome 15. The disorder causes relentless deterioration in brain and muscle function, leading to death around 3 - 4 years of age.

Stem cell. An undifferentiated cell that gives rise to differentiated or specialised cells.

Gene therapy. The introduction of DNA into the cells of humans, or the introduction into humans of cells whose genetic material has been modified. First approach involves use of a gene carrier or 'vector' (often a defective virus) to carry a gene into cells and integrate the gene into the cell's DNA. Aims to improve health.

OVERVIEW OF PRESENTATION

Molecular Medicine

The impact of genomics and cell technologies on the future of medicine, healthcare and the economy – opportunities, challenges and issues for Australia

Overview, Introduction

We are in the early phases of one of the most important periods of discovery in human history – the exploration of the genetic basis of life and its diversity. This is referred to as Genomics. The differences between individuals, and between limes and lemons, are embedded in the details of our genetic programming and inheritance, although this is also affected by environmental factors. Plants and animals contain between 10,000 and 50,000 genes, each of which encodes one or more proteins, which in turn form the basis of cellular structure and biochemistry, and which form the complex networks which underlie growth, development and physiology.

Those who decipher and utilise this information effectively (and competitively) will transform and dominate all of the biologically-based industries in the coming century – clinical medicine, pharmaceuticals, agriculture, natural products, waste treatment and environmental management, among others, and which account for around half of the total world economy – as well as generate entirely new industries and opportunities.

For these reasons, Genomics is now widely regarded as the third great technology revolution, after the Industrial Revolution and Information Technology, and this field and associated areas of advanced molecular and cellular biology are attracting massive public and private investment in the US, Canada, Europe (UK, France, Germany, Sweden, Ireland, Iceland, etc.), Japan, China, Singapore, Taiwan and other places. In all of these cases, strong public investment has been the strategic platform (generating knowledge and enabling technologies) for much greater subsequent private investment and industry development, which in turn leads to economic growth, as has occurred in information technology.

The first stage of the Human Genome Project (the DNA sequence, over 3 billion bases) has now been essentially completed and was recently announced by US President Clinton and UK Prime Minister Blair. This is just a template for analysis of our genes and their normal roles, and for investigating the effects of the many differences between us on our health and potential. The NHMRC recently arranged access to this data through an agreement with Celera Genomics Corporation, the first of its kind in the world. Although this has come at considerable financial cost, the outcomes illustrate that even at this relatively early phase of the genome race that those who do not reap the rewards will pay for access to them, and much more dearly for access to the medical products and services that follow.

The genomes of many other species, including model organisms such as yeast and fruitfly, and many pathogenic bacteria and viruses, have also been completed, and many more, such as mouse, cattle, horses, fish, malaria, and various plants (to name but a few) are underway. However, this is just the beginning of a great period of genomic exploration, and there remain many opportunities for Australia. Ultimately the genomes of all organisms of scientific and practical interest (primates, chickens, prawns, ticks, rabbits, eucalypts, strawberries, unusual microorganisms, etc.) will be sequenced, as the basis for advanced applications in medicine and biotechnology.

These organisms share many genes in common, and are important to understanding human biology, the nature of biological diversity, and the molecular basis of both genetic and infectious disease.

The next phase is referred to as 'functional genomics' and involves connecting genomic information to the biology. This will be a significant task, and will involve re-sequencing of human and other genomes to understand the differences between individuals, as well as the intensive use of computers to store and analyse genomic and experimental information, and to model cellular and physiological systems for advanced applications, for example in drug target selection, drug design and in silico testing. Bioinformatics and computational biology is an emerging field of crucial importance to the next generation of biomedical science and biotechnology. These fields are also being accelerated by, and interfacing with, advanced optical, computer chip and nanotechnologies, as well as the recent advances in chemistry and cell biology. The pace of change is enormous.

In the first place, this will lead (and has already led) to an explosion of new knowledge and a progressively fuller understanding of the genes and genetic differences between us (and consequentially the biochemical, cellular and physiological processes) that affect our health and well being, including those involved in:

- important genetic diseases such as cystic fibrosis, thalassaemia, Huntington's disease, and haemochromatosis
- cancer and cancer progression,
- common diseases affecting large portions of our population, such as asthma, diabetes, hypertension, Alzheimers, glaucoma, pre-eclampsia, etc.,
- pathogenesis and susceptibility to bacterial and viral infection, and
- our normal physiology and development, including embryogenesis, brain development and aging.

In addition recent advances in stem cell biology and cloning have opened up new and unexpected possibilities for the repair of diseased tissue. The intersection of genomics, gene technologies, cell technologies, optical technologies, biomaterials and information technologies is creating new vistas and is driving the development of innovative new industries, many of which are yet small, but some of which will become large enterprises, as happened in the computer revolution. This requires the right mix of discovery, ideas, technologies, venture capital and innovative well trained people.

It is hard to convey the scale and full extent of what is happening, nor accurately predict its course. However it is important to appreciate that new knowledge is the key to all of the practical applications and the commercial opportunities to follow. If we do not invest in this, and compete with others who are off and running, our ability to reap the benefits for Australia will be limited. The experience of the United States is instructive, as in that country the development of high technology industries has been underpinned by massive public investment in research, which has been aggressively taken up by industry, often in the form

of start-up ventures (including Microsoft, MacIntosh, and Celera Genomics Corporation). Other smaller countries which do not have Australia's traditional research strength, such as Singapore and Ireland, are making large investments in education and research, focused on information and communication technology and biotechnology, accompanied by tax incentives for industry and individuals, in an effort to join the advanced economies, with great success.

Medical Applications

New pharmaceuticals, vaccines and antibiotics

- Therapeutic hormones produced by genetically engineered bacteria and which have lifesaving benefits in the treatment of (e.g.) diabetes and leukaemia (insulin, GM-CSF, EPO – it is also worth noting that the international market for these three pharmaceuticals exceeds the entire value of the Australian grains crop).
- New drugs against important target proteins (identified by genomics) produced by screening of natural or synthetic chemical libraries (such as new pain relieving compounds), or by computer-aided design, which are can modulate biochemical processes to reverse or prevent illness, such as asthma, hypertension, depression, neurodegenerative diseases, and cancer.
- New immunological and gene-based therapies for the treatment of cancer and auto-immune diseases.
- New antibiotics (as an alternative to conventional antibiotics and a solution to the rising problem of antibiotic resistance) and new antivirals (to treat untreatable diseases) produced by chemical screening or design against novel targets identified through genomic analysis.
- New vaccines, based on the production by genetic engineering of key antigens (e.g. hepatitis B vaccine) and which avoid many of the safety and cost problems associated with traditional vaccine production.

New diagnostics

- Diagnosis and prognosis of genetic diseases to allow early prevention or treatment.
- Diagnosis and prognosis of cancer, cancer susceptibility and cancer progression to inform surveillance, treatment and treatment options (e.g. breast cancer, colon cancer, prostate cancer).
- Diagnosis and prognosis of genetic differences that affect susceptibility to common diseases to allow early prevention or treatment (e.g. asthma, stroke).
- Determination of transplant compatibility.
- Pharmacogenomics – individual prediction of unwanted side-effects and the most appropriate treatment and dose.
- Diagnosis of infectious disease and its likely severity, as well as the best treatment regime (e.g. hepatitis C, food poisoning).

Genetic therapies

- Gene therapy, while still experimental, holds much promise for the treatment of genetic disorders, many of which are rare, but which collectively affect a large section of the world's population.
- Gene therapy has recently emerged as a possible alternative form of treatment for cancer and HIV, as well as for the treatment of more common diseases that may have environmental causes. Promising results have recently been obtained in the treatment of immunodeficiency and haemophilia. (However, at present Australia is very much dependent on overseas sources for gene therapy vectors, a potentially costly position for the future.)
- Very powerful new RNA technologies are emerging which will open up radical new approaches to treating viral diseases and cancer.

Cell therapies

- Although still in a very early phase, stem cells are emerging as an area of enormous potential for tissue repair and regeneration, in the treatment of burns (skin replacement), heart disease, liver disease, neuromuscular disease, neurodegenerative diseases (such as Parkinson's disease) and other diseases associated with aging.
- Ethical controversies may be reduced by new advances, such as re-programming of our own cells, rather than requiring embryonic sources.

Impact and Outcomes

The economic potential of this sector and its public acceptance are both directly related to the perception by the consumer of the need, value and safety of the new products and services developed through biotechnology, in all of its manifestations. Nowhere is this better illustrated than in medicine, where genetically engineered pharmaceuticals are widely used and accepted. These products are safe and effective. Equally, the acceptance or otherwise of other applications, such as genetically modified foods (where most of the current opposition is ideological rather than practical) will depend on confidence in quality and safety, but there is as yet no strong incentive to use these products as the value to the consumer is not (yet) obvious, although producers can see value for example in the reduction of insecticide use. However, this is just early days, and there are many developments to come, especially in health where the imperatives are strongest.

We will see the rise of personalised medicine, whereby knowledge of a person's own genetic status will enable areas of risk to be identified and avoided or treated, as well as the individual tailoring of treatment regimens and drug doses, thereby improving the outcomes of treatment and reducing the medical and financial costs resulting from drug toxicity.

We will see a radical change in practice of medicine from the management of established illnesses to preventative maintenance, through genetic diagnostic and prognostic testing, and a wider range of pharmaceutical, cellular and environmental therapies.

This will result in a net positive impact on health economics through reduced hospitalisation and more intelligently targeted expenditure, and reduction of the health burden of our population.

It will also lead to a positive impact on quality of life.

There are very substantial opportunities for Australian pharmaceutical, diagnostic and biotechnological industries, and a reciprocal threat to our healthcare budget and balance of payments if all is imported.

There will also be many lateral and often unpredictable opportunities and spin-offs for other industries (nanotechnologies, artificial organs, biosensors, biocomputing)

Issues and Challenges

This is the best opportunity for foreseeable future for Australia to participate in the formative stages of a new scientific and technological revolution and a major knowledge-led industrial transition.

Australia is one of the ten or so best countries in the world in biomedical research – failure to convert this into a strong position in the new world of advanced medicine will cost dearly in terms of lost opportunities and negative balance of trade. The race is on, but we are falling behind. Our scientific and educational base is historically strong, but has declined in recent years, and many of our best people are overseas. Of the top countries in biomedical and agricultural research, Australia is the only one which is not investing heavily in genomics and related areas such as bioinformatics and cell technologies. Canada, for example, has recently announced a \$160 million investment in large scale genomics projects (Australia has just over \$4 million allocated for such projects in 2000).

Australia is a small country, for which it must compensate by being as strategic and focussed as possible, especially in times of opportunity and rapid change. Other smaller countries that do not have our traditional strengths are doing just that and are rapidly going past us – Ireland (about 20% of Australia's population) has recently increased its basic research budget by \$1 billion per year, with 25% going into a new science foundation (Science Foundation Ireland) focussed on information technology and biotechnology. Singapore (around 10% of Australia's population) is committing around \$1 billion a year in these same areas, and is now emerging as the likely capital for biotechnology in the Asia-Pacific region. Moreover, Singapore is starting to attract massive international investment from Europe, the United States, Japan and China, at the expense of Australia. Singapore still lacks the skills base and depth of Australia, but it will not be long before this is overcome.

There is an urgent need for forceful public and private investment in genomics and related areas, including bioinformatics and computational biology – public investment is needed for the strategic platform, and private investment is needed to convert the knowledge and technology base into new industries. The US government is currently spending ~\$US20 billion (\$A40 billion) on basic biomedical research per annum and this is increasing, underpinning even greater private investment – US biotech companies are strongly outperforming NASDAQ despite understandable volatility.

There is an urgent need to reverse the brain drain. We need to attract (and retain) key personnel with research and business excellence, on the basis that we are serious about being a player in this area and in the development of a knowledge-based economy, as evidenced by government commitment and leadership. This could also include internationally competitive research fellowships, personal and corporate taxation incentives, seed funding for new ventures, and inducements for relevant firms to relocate regional and head offices and production facilities to Australia. If these settings are right, Australia's lifestyle advantages and stability should give us a significant competitive edge, as this is an important secondary factor for an increasingly mobile capital and high technology community (for example San Diego, Seattle).

We need new education programs in cross-disciplinary areas such as bioinformatics, computational biology, biomaterials, bioelectronics and bioengineering, as well as (perhaps compulsory) courses in intellectual property management for graduate students.

We also need to engage and educate the public, and address key issues (esp. in reproductive technologies), with an appropriate regulatory and ethical framework in place (AHEC, Gene Technology Bill 2000). There is a range of ethical issues emerging as a result of developments in this area, these include sensitivities surrounding genetic testing and embryonic stem cell research.

Health professionals must also be educated to ensure the rapid transfer of new information and new treatments as well as efficient use of health resources.

We should continue the good use of existing regulatory frameworks and bodies, but ask that costs should be waived by regulatory bodies for publicly funded research (as opposed to product licensing), as to impose charges will slow down and reduce the effectiveness of our research base.

We need vision and courage. We need strategic investment in order to respond to the challenges that lie before us, and to consider the approaches being followed by other nations such as Ireland. We also need engage in strategic planning to be competitive in genomics and molecular medicine, and to anticipate and prepare for changes in medicine, clinical demographics and health economics that will follow, both to take full advantage of the opportunity before us and to deliver the best economic and health outcomes for the people.