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"THE BIOLOGICAL REVOLUTION"

by

THE GOVERNOR OF VICTORIA,

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THE GOVERNOR PROFESSOR de KRETSER: Thank you, Maryann for that introduction. I wondered what you were going to say about the "grumpy old men". I had thought about talking about men's health because there are some issues there which are of interest. But it is always difficult when you're talking to a group of professionals who come from different disciplines. You have to walk through a narrow pathway so that what you say is intelligible to all of them. I'm told that there are more medical than legal people here tonight, so bear with me if some of these things are things that you're familiar with because I have to take the lawyers along with us as well.

When Gabriele asked me about this some months ago I gave her this very broad topic that becomes more problematical when you sit down to write it.

I really feel that we are living in a phase which will be known as the “biological revolution”. If I said to you “what about the “information technology revolution” you would probably all now have a very clear idea of what that is and what changes it has brought to our society. However what we're facing at a time when our knowledge and practical development in the biological sciences and in medicine are poised to really change our society in a multitude of ways, is not so clear.

There has been a real explosion of knowledge in biology, and I would like to discuss with you just three areas which either have, or will provide remarkable changes in our society in the way we handle a number of issues. The first of these is the discovery in 1953 of

the structure of DNA, the molecule that is responsible for transmitting genetic information from one generation to another, the molecular basis of inheritance. The availability of that information really then led to the definition of DNA sequences, the identity of genes, the ability to isolate or, as we call it in "the business", to clone a gene, in cloning a specific protein, and then the ability to alter the DNA of that gene which in turn can lead to a different sort of protein. That starts to give you some ideas of how important that protein is and what it can actually do.

I guess the “holy grail” of identification of a code of DNA was really the sequencing of the human genome in its entirety for the first time, achieved in 2003. 50 years elapsed between Watson and Crick's identification of DNA structure and the sequencing of the whole genome. The second major development was the technology that enabled the fertilisation of an egg by sperm outside the body, namely the process known as “in vitro fertilisation” which has revolutionised the management of both female and male infertility. This discovery led to the capacity to store embryos frozen, to split embryos and to fertilise eggs by the physical insertion of a single sperm known as “intra cytoplasmic sperm injection”, or shortened "ICSI".

The third is partly linked to the second, and that is the isolation of stem cells from embryos and adult humans, with a capacity to clone an entire mammal, technologies that are still in their infancy but really with limitless potential. There may be others that you might choose, and the potential of each of the above set of discoveries

is greatly augmented by technologies that are developing in parallel in other sciences: in information technology; in nano technology; in material sciences and physical sciences. If you just think about it, if you're going to put stem cells together to create potentially a new tissue or an organ you need to have a support system and the physical scientists are actually finding those support systems that are eminently capable of doing that. Let's just take each of these areas and talk a little bit about the potential outcomes and the dilemmas that emerge. Our understanding of the structure of DNA led very early to very laborious techniques to sequence a DNA code of individual genes. When these were combined with our knowledge of chromosomes, the structures on which DNA sequences are arranged, and the alterations in chromosomes in families with pedigrees indicating inherited diseases, slowly links between specific genes and particular diseases emerged. Then through the sequencing of the entire human genome, which identified the structure of approximately 30,000 genes that comprised the human genetic code, many practical developments have occurred.

In fact this landmark study would not have been possible without parallel developments in chemical technology that created the machinery to be able to sequence the DNA and to identify the code, and if you didn't have the power of modern computers it would really not have been possible to store the information, analyse it or interpret it. If you were to print the sequence of the human genome it would fill 200 volumes each of 1,000 pages, and it would take nine and a half years to read it

aloud working 24 hours a day. It took 13 years for a consortium of scientists around the world to sequence and analyse the data comprising the human genome. And since that time, 2003, the speed with which instrumentation has improved means that today we see in the scientific journals the whole genome domestic species, insects, plants, all adding to a huge amount of biological information.

It is likely that those of you who are sitting here and who survive another ten years could walk into a laboratory, maybe Gabriele's laboratory in ten years' time, give a blood sample and have your individual genome sequence within a week.

What does this mean for mankind? It means that we can define the genetic basis of disease, the changes in the DNA code of individuals which cause a specific disease entity and that knowledge enables us to develop new diagnostic tests for that particular disorder. What do we do with that information? If a person has a family history of Huntington's disease, a genetically inherited disease that causes irregular movements of the body and progressive dementia, presents its first symptoms in adults. Should they have the genetic test that can warn them of the outcome well before they show the symptoms? Information that would enable them to plan appropriately and decide that they may not wish to have children, to remove any risk of repeating that disorder. Alternatively, they may wish to have IVF and to take a single cell from a developing embryo to test it for the disease and then only use the unaffected embryos. Is that ethically okay? I'm not going to answer these

questions, I'm just posing them.

If they do have the genetic information before the symptoms present should they rush off and take out a high level of health insurance? Are they duty bound to advise the insurance company about the disorder and the outcome of the results? Is it fair that the insurance company refuses to insure them or loads their premium? How about a hypothetical that's a bit more complex where, say, recent discoveries just emerged in a journal might have identified a gene that can make people susceptible to develop lung cancer if they smoke. Should this be then a compulsory test for everyone before life insurance is taken out? If the test is positive should the person's life insurance become invalid if they smoke tobacco? Interesting questions!

Let's consider now for a moment the continued development of this field. We still do not know the function of all of the 30,000 genes that have been identified, and one of the technologies that assists us in finding out information about the function of a particular gene is to knock out that gene in a mouse and see what happens. This is a very powerful technique which involves using mouse embryonic stem cells which have been available for nearly 15 years and it's possible to pick out a particular gene that one's interested in and manipulate its DNA structure in such a way in a test tube so that when the modified gene is reintroduced into a mouse embryonic stem cell it can actually knock out or inactivate that gene. You can then take that modified embryonic stem cell and put it into a mouse embryo, and it therefore contributes to that mouse embryo when it's

put back into the uterus and allowed to develop so that these mice that are born with this defective gene can then be studied to identify what defect arises as a result of that gene.

For instance, the gene may make male mice infertile because the sperm are created immotile. Sperm motility is essential for sperm to reach the site of fertilisation, penetrate the egg, and to fertilise it. This information could then lead to diagnostic tests for infertile men. If they have that disorder should they be allowed to reproduce using IVF methods in which sperm can be injected directly into the egg? Alternatively, having identified the gene, if new drugs could be developed to target this defect and to overcome it should these men be allowed to reproduce knowing that they will be adding disordered genes to the human gene pool? I think personally that such a principle is untenable but it is raised from time to time in discussions.

Another approach to solving problems is using information from other species from which the genome has been identified. I want to tell you about a little single organism. Those of you who have done medicine will remember doing biological practical classes in which you looked at a single cell algae, (chlamydomonas is its name), which had a tail and swam, just like a sperm, using its tail for propulsion. With the electron microscope,the structure of the algae and the sperm, magnified 100,000 times look very very similar.
This is the background of a human problem. About one in 10,000 men are infertile due to their sperm being totally immotile. Interestingly, that disorder is combined with

a chest disease called bronchiectaasis where the lungs become continually infected and parts of the lung have to be removed. About 50 per cent of those men have their heart on the right-hand side of the body instead of the left, and some of these also have their appendix on the right-hand side. In other words, their whole axis of development is altered. Some are also congenitally deaf. So how is this related to the single cell organism? The lining of the bronchial tubes in your lungs and, indeed, your sinuses, have moving projections, like small hairs on their surfaces, called cilia that move in a coordinated fashion causing secretions on the surface to move in an "upward" direction, that assists you in getting "junk" out of your chest and coughing it up. If these secretions can't be "moved up" they stagnate and get infected causing progressive damage to the air passages, resulting in bronchiectaasis.The structure and functions of the sperm tail are very similar to the cilia in the respiratory tract. The gene that causes this defect was very very hard to pin down, so what they did was to take chlamydomonas, which breeds very rapidly, and it's very easy to tell whether one's swimming or not swimming, and segregate non-swimming populations. Since the gene sequences of this species is known they were able to identify the gene that caused this immotility of sperm. They took that information and they went to the human genome, and since there is a 70 per cent "identity" between the gene sequence of DNA and chlamydomonas, the particular gene that turned out to be involved in causing this problem of immotile sperm and immotile cilia was the same. Indeed an incredible degree of "conservation". It

is obviously a very important function to be able to move cells and to have movement at cell surfaces that survived over that evolutionary period of time.

A very practical and far-reaching approach from the genome explosion is much more commonly known probably to you: the production of human proteins for therapeutic uses in bacteria, or mammalian cells that are suitable genetically engineered, creating a factory in these cells or bacteria. For instance, the identification of the sequence of the gene that encodes hormones such as insulin enable biological factories to produce human insulin which, obviously, is critical in managing insulin deficient diabetics. Insulin used to be purified from the pancreas of pigs or cattle but now bacteria or mammalian cells in culture are genetically programmed to manufacture human insulin.

It is interesting that this approach is not too dissimilar from how you might genetically engineer a crop. We accept the one as a human therapeutic, but we have reservations about other. In the area of cattle breeding there has been a natural genetic modification of a gene called myostatin which actually limits muscle growth. A mutation in this gene this resulted in the development of the Belgian Blue, a breed of cattle which has huge muscle development. Farmers bred those animals by selective breeding for specific traits of big muscles over a long period. Today you can actually make a "muscle mouse", a mighty mouse, just by changing that gene in the mouse.

Let's turn now to that second area of in vitro fertilisation developed originally to enable the sperm

and eggs to meet in women who had blocked Fallopian tubes. Fertilisation occurred outside the body and that the first birth was in the UK in 1978. This technology has now advanced to the point where such women under the age of 37 can be offered consistently a 40 per cent per attempt chance of achieving a pregnancy.

Extensions of this discovery, as I mentioned earlier, led to the ability to isolate sperm, simply by inserting a very fine needle into the testis, physically take a single sperm, and fertilise the egg by puncturing the outer wall, thus removing the physical barrier for sperm penetration.(ICSI) This technique enabled the services to be extended to those couples where the sperm and the egg don't "recognise" each other probably due to abnormalities of "sensors" or receptors on the surfaces, much like the recognition occurring between people on the basis of facial features.
When that recognition fails, or if a man has antibodies to sperm that "coat" the spermatozoa, (which occurs in 70 per cent of men who have a vasectomy),the sperm will fail to detect the egg.
ICSI has made a huge impact in the management of male infertility, and now nearly 50 per cent of all IVF that is carried out is to assist infertile men and their partners. It can assist men with sperm that are not moving; it can assist men where the sperm count is too low for standard IVF. It can also assist men who have an obstruction of the tubes that lead spermatozoa away from where they are formed, in whom no sperm are found in the ejaculate. This may be a congenital problem, or there may have been a vasectomy, or sometimes sexually

transmitted disease may cause obstruction. It's very difficult micro-surgery to reverse obstruction in those tiny tubes, and the success rate is not high.

Clearly these techniques have made a huge difference, and further development has resulted in embryo freezing, embryo splitting and so on. Egg donation enabled women who were past the menopause or who had had a premature menopause to have an egg donated and to achieve a pregnancy. However these technologies are not free of ethical dilemmas. From the ethical standpoint, is it reasonable that a woman who is 60 years of age should be allowed to have that technology? It's a very hard question to answer.

For some, religious beliefs mean that the use of any form of assisted reproductive technologies is not acceptable. But on the whole the routine use of IVF is free of major ethical constraints other than those of technology competence, and the issue that it does have some side effects such as over-stimulation of the ovary, and the tendency of IVF derived babies, particularly in the case of multiple births, to deliver prematurely.

There is also an issue of safety in the ICSI procedure. So far this technology is about 13 years old. There have been no dramatic difficulties except that men with very low sperm counts have a slightly increased risk of a genetic abnormality identified in the children born with ICSI.

One example is an increase in the risk of a baby having Down syndrome. Normally about one in 2,500 live births, this risk increases following ICSI to about two to three per 2,500 births, and there is a similar increase in other disorders in which there is an alteration in chromosome

number. This has actually now been traced to defective sperm in which the chromosome numbers are altered, rather than the physical disruption caused by the technique. A child with Down Syndrome has three copies of what we call chromosome 21, whereas you or I have two copies of chromosome 21: one that came from your mother and one that came from your father. During the production of the sperm, those two copies that a male has go to different sperm. In the men who have a problem with sperm production those two copies may stay together so that you might have one sperm with two chromosome 21s. If this sperm meets an egg which has one chromosome 21 the resulting embryo will end up with three, and that baby has Down syndrome. There is probably no easy way of dealing with this problem.

Another clearer example is that men have a Y chromosome and women don't and in men who have sperm counts of less than five million something like to five to six per cent of the sperm have a defective Y chromosome that has "lost" genetic material that is the cause of their infertility. If a man fathers a son through ICSI his son may inherits his deficient Y chromosome and be infertile when he matures, but we cannot be sure of that yet because the technology has not been in practice long enough. There are only about 15 or 16 variations of the Y chromosome and it is actually possible to trace heritage back through a number of generations by identification of such genetic variation. It is still too early to say whether there are other genetic causes of infertility which we don't know about which might have side effects other than male

infertility.

We have on occasions told couples whose male partner has a Y chromosome deletion "You could actually have a cell taken out of the embryo and if it's a female embryo transfer it and if it's a male embryo don't transfer it, that's legal in Victoria". However the couples that I have dealt with have said "No, doctor, you're helping me now, you'll help my son in 20 years' time, hopefully". There is another interesting area that has been studied in animals The genetic material of a sperm is packaged into its head in such a way that it's remarkably stable. You can actually boil a sperm for 30 minutes and it won't move any more but if you take that sperm head and inject it into an egg you will get a normal offspring. The Japanese have even gone one step further. Researchers took a block of tissue that had been taken from the testis and had been stored, I think fixed in alcohol, and put into a paraffin wax block. Pathologists cut a section from the block to look at, then removed all the wax from the block and took a sperm from that tissue, injected it into a cow egg, and achieved a normal calf. It is food for thought that all the repositories of testicular tissue stored in pathology laboratories could potentially provide sperm that might end up with pregnancies from people who are now long gone. This is not permitted by our law at the moment.

Let me turn to the last technological advance I want to talk about, stem cells. We have had stem cells from the mouse for 15 years, but it has been very hard to identify and make stem cells from the human. Stem cells have the potential to give rise to any tissue in the body

and therefore this technology has immense promise. So what can I add to a debate that was played out in the press and in Federal Parliament not too long ago?

I would just like to clarify a few of the concepts, because I found the debate was very confused. We had protagonists and antagonists; proponents and opponents who used emotive languages and sometimes the points didn't get across. There is no doubt that the potential use of stem cells has captured the public imagination because of the possibility of potentially novel methods of treating a variety of diseases that affect both young and old. It has of course also captured scientific imagination and there is a huge amount of research going on. While there is still uncertainty as to whether the technology will deliver fully, it must be remembered this field is really in its infancy.

So, let's just consider what is a stem cell? A stem cell can be defined as a cell that has the capacity to maintain itself by replication and also give rise to daughter cells that have the capacity to become - or we in the parlance call it "differentiate" - into more specialised cells. And the variety of cell types that a stem cell can form defines its potency or its capacity. Some cells are totipotent, meaning they can give rise to every cell in the body such as occurs during normal development. Others can only give rise to a limited set of specialised cells although those cells still have the same genetic information as the cell that can be totipotent. It is obvious that as cells specialise, somehow their genetic material is limited in the way it can express itself and give rise to all cells of the

body. We don't really fully understand, for example, what it is that makes a skin cell only be a skin cell, and why it's genetic material is hidden or can't be expressed in such a way that it can give rise to totipotent stem cells. Probably the only truly totipotent stem cells are the first four cells in the embryo, after that there is a restriction on what they can produce.

It is possible to make an "embryonic stem cell" line from an embryo that is not being used for IVF because the parents have decided that they have enough children. That cell line can be maintained under development, dividing, but it can be prevented from becoming a specialised cell. These cells are actually immortal, so they keep on going so long as they are looked after appropriately.

On the other hand, stem cells with limited capacity or potency can be isolated from adult organs. They are called "adult stem cells" but the number of cell types is actually small and they do not have the capacity to become totipotent. The adult cells that come closest to being totipotent are cells that are found in some tumours of the ovary and the testes which are called teratomas. A teratoma apparently arises from a deranged totipotent cell that can make a large range of tissues and such tumours have been used to study the process of differentiation.

Scientists are looking for methods to remove the controls of adult cells to make them totipotent and that's a process called "somatic cell nuclear transfer" sometimes it's also called "therapeutic cloning",because the embryo can give rise to a cloned organism. Dolly the

sheep was created in just that way. A breast cell was taken, its nucleus was exchanged with the egg of a sheep, and that removed the normal controls on that breast cell that enabled Dolly to develop.

There is an ethical dilemma that commences with the question whether such an embryo the same as the embryo that's developed naturally through the fertilisation of an egg and sperm? Is there a right to equate a totipotent cell with an embryo? Not in my mind but each person has a different view.

Is there any way to define this issue further? A natural embryo is formed by a sperm and an egg coming together containing material from mother and father to create a genetically unique individual. There is no way that taking my cell, and removing all of its controls and making it totipotent, can create a genetically unique individual. It is a replica of me.

This is one way that I can deal with these issues in terms of trying to understand and separate and provide some clarity in consideration of this important ethical dilemma that many people feel that they have.

Whereto from here? Clearly, there's a diversity of views on this topic but one must question whether they are based on an understanding of the terms in this complex but wonderful field of biology. I'm continually astounded at the speed with which developments are occurring.

I'm sure you're going to hear about a lot of those in the future with a lot of potential questions.

Already there's a group in Japan who have taken an ordinary adult cell in the body of a mouse, inserted four

genes which are known to be involved in early development into that adult cell, resulting in removal of all the controls so it became, an embryonic totipotent mouse cell that then gave rise to normal offspring, without the use of an egg. It's not yet established whether this could be done in other species. However people are analysing what is actually in the egg that makes it so special, and I would predict within five years it will be possible to manipulate an adult fibroblast or skin cell and drive it to make insulin-producing cells for a diabetic, or growth hormone cells, if you're a short person and need growth hormone, or cartilage cells if you happen to be an athlete that needs some new cartilage.

The last issue that I leave with you is that all of these technologies offer the capacity to extend our life span even further, which will further explode the world's population that at the moment is increasing by 200,000 people per day. No doubt this will compound the issues of carbon dioxide emission as we need more energy with the obvious issues of climate change. With that sobering comment I will leave you to think about the ethical dilemmas that might arise. Thank you.

Questions:

DR NEALE: I am Bernard Neale and I am a member of the medical profession. Thank you very much indeed for that wonderful speech. Re the very last point you raise how might the biological revolution affect these universal human phenomena of ageing and mortality which engage some of us very acutely? I read recently an eminent scientist

speculating whether the present generation of our grandchildren would be the first generation to live forever or the first generation not to do so.

THE GOVERNOR PROFESSOR de KRETSER: Well, that was the question I was hoping you were going to answer. We progressively have new medications even without some of these developments that I'm talking about which are extending life span and it is a crowded planet. One really has to ponder these issues of how available are all these techniques going to be, where will they lead us? It's very hard to say you should restrict that development or allow this one. I think we just should be conscious of this issue as a society when we think about it, because not all of the developments and discoveries are easily affordable and that does raise again some issues of equity. And if you get into the climate change issue, do we have the right to expend more energy than a subsistence farmer in the back blocks of India.

DR MARSHALL: Robert Marshall, medical. The current debate that's been going on, Your Excellency, has been about more than anything else stem cells. My question is has there been any work done on taking cells from one animal (like me), say a skin cell, and implanting the nucleus into the ovum of another species and if that were done would it produce stem cells, would it produce a clone,

THE GOVERNOR PROFESSOR de KRETSER: Thanks, Bob. I don't believe it would form a clone. I can't answer that with certainty. The easiest way is to say we're not allowed to do it and I don't know of anywhere else where it is being done but I wouldn't put it past somebody to do it with a cell line or something like that. I don't know.

I just don't know. I mean clearly to function that cell which has your skin cell nucleus in it would need to have a cellular machinery that is compatible with keeping that cell alive and I don't know whether that's feasible because mitochondria have DNA in them which again may lead to difficulties. I think it's much easier to work out what it is in the human egg that's necessary and it will be very similar to what's in the mouse egg and in any other species because these things tend to be conserved very highly through evolutionary processes, so we will be able to learn from other species, there's just no question about it.

DR YATES: Mark Yates, medical. Your Excellency, thank you very much. I think many doctors here would be aware that chlamydia infection in women is the common cause of infertility and in fact possibly up to 25 per cent under the age of, say, 22 have asymptomatic infections with chlamydia which we don't screen for routinely terribly well at the moment. I just wonder if as we go headlong into the biological revolution we will miss opportunities or lose some of the opportunities that that might have to offer if we don't also address issues of public health. I sense a tension between the sudden need to get a genetic answer for everything, rather than addressing it at a public health level, when I think that the latter may actually provide greater outcomes for the population than the former.

THE GOVERNOR PROFESSOR de KRETSER: I would agree with you entirely. I believe that the reproductive technology should only be used when there is the absolute need to be done, when the patients have been thoroughly investigated

and all causes, including chlamydia, have been excluded. Certainly, some of the major things that could be done in some of our communities here in Australia, particularly in the indigenous community, such as getting rid of chlamydia and managing it and many others, even simpler, if you think about the global state of medical care. No argument at all.