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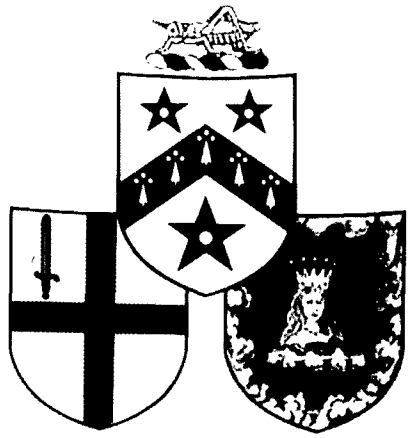

CONFLICT AND CONSENSUS IN THE AGE OF THE NEW GENETICS

Lecture 6

GENE THERAPY FOR BATTERED BRAINS?

by

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Gene Therapy for Battered Brains?

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The programme for each year's Gresham lectures is set the preceding spring. But the speed of biotechnological advance is currently outrunning such a normally proper pace for advance planning. "The new technologies of genetic engineering," we wrote last year in the summary of today's talk, "offer to replace or modify 'faulty' genes. Somatic therapy is intended to correct the genes only in the patient being treated; germ-line therapy - currently illegal - will alter subsequent generations too. Can such treatments be developed to cure or prevent Alzheimer's, Parkinson's or Huntington's diseases, or even rectify the damage caused to brains by stroke or accident? And if so, what are the ethical implications?

Since we wrote that synopsis, there have been at least three major developments.

1. First, the British government has legalised stem cell research – the first country in the world so to do - and against a barrage of ethical criticism.

2. Second, experimental clinical procedures designed to mitigate the effects of Parkinsonism by injecting foetal material into the brain have gone badly wrong and have been terminated.

3. Third, a group of clinicians and researchers have held an international meeting in Rome to announce their intention of proceeding immediately with human cloning.

These three developments form the background against which we need to consider the issues touched upon in our original plan for this talk. By way of recap, we should emphasise again the difference between somatic and germ-line gene therapy. In essence, it is argued, somatic gene therapy is no different in principle from any other sort of pharmaceutical intervention, except that the 'drug' that is administered is a DNA sequence designed to replace or substitute for an absent or faulty gene. We can debate whether this claim of equivalency is ethically justified; but anyhow, as we have pointed out in earlier lectures, until now somatic gene therapy simply hasn't lived up to its expectations. There is just one modest success story, reported a few weeks ago, for a rare immune deficiency disorder, but the general record has been dismal -and in one case in the US, where regulations were flagrantly breached, has led to the death of a volunteer patient.

To see why it has proved so problematic, we need to consider the problems of getting it to work, even after one has identified a specific gene defect and generated the DNA intended to correct it. The DNA has to be packaged in such a way that it can enter the appropriate cells without being broken down, and then become incorporated into the existing genome, where, it is hoped, it will now be translated into the protein which the deficient cell lacks. This is a problem in itself, as gene regulation is a very highly organised and controlled process; the exogenous DNA runs the danger of being a spanner in a very complicated set of works. But the first problem is to get the DNA into the cell to start with. To do this, genetic engineers need to package it appropriately. One method is to wrap it into a little lipid package, called a liposome, which can be taken up through the cell membrane - a route that has been tried for cystic fibrosis. But the more general approach is to insert it first into a modified virus, and as viruses generally work by entering the cell and subverting the cellular genome, it is hoped that the engineered DNA will do the same. It is clear from this description though, that there are considerable problems in getting this process to work. Even before the packaged exogenous DNA can begin to function, it has to be got into just the right cells in the already developed body, and there may be hundreds of millions of these. Just to get it into a few

won't suffice; equally, getting it into the wrong cells may mean that they also begin synthesizing the wrong protein - that is, a protein not relevant to the functioning of that particular cell. The adult human body has some 250 differently specialised cell types, each normally expressing just a fraction of the tens of thousands of different proteins into which the gene fragments in the genome can be translated and edited.

The viral machinery is pretty sophisticated, but genetic engineers can't tailor it to the precise purposes required. So it is not perhaps a great surprise that despite all the hype which has pushed up expectations over the last two decades, somatic gene therapy is still not going anywhere very fast.

This helps explain the pressure from some in the medical and biological research community, especially in the US, for permission to breach the ban on germ line therapy. Modifying a gene in the nucleus of a single egg or sperm cell is now well established technology in plant and animal research, and presents few of the technical problems of working with adult cells. Just one cell has to be modified, and the modification will be carried through into all the trillions of somatic cells during cell division and development. Many of you will remember the 'green fluorescent monkey' which hit the headlines a few weeks ago as an example of how this can be done (this will be discussed). But of course, modifying a germline cell means that all the offspring of the person carrying that modification will also carry it, and this has been the ethical line in the sand that has been drawn so firmly hitherto.

And this is where stem cells come in. During the early stages of development, as the fertilised ovum begin to divide, the daughter cells remain, to use the technical term, totipotent - that is, they continue to be able to express all the proteins of which the genome is capable. During development this capacity is steadily lost. As the cells begin to differentiate, and form the progenitors for brain and muscle, heart and kidney, they move from being totipotent to multipotent and finally to the fully specialised adult form. Fully developed, adult cells have shut off much of their genome, so that only the proteins relevant to that cell's function are expressed. Until recently it was pretty much dogma that once this transition had taken place, it was irreversible; there was no way back - at least for mammals. Many plant cells by contrast, remain potentially totipotent throughout their life, which is why cloning plants is easier than animals. It is the early embryonic totipotent or multipotent, cells which are the focus of the current controversy. These are the ones known as stem cells, because it is from them that all the body organs are derived.

It used to be believed that there were no stem cells in adult fully differentiated tissue - except in bone marrow, responsible for the production of the many types of blood cell. However, after the cloning of Dolly the dogma no longer holds: it may be possible to regain totipotency, and indeed some stem cells may be present in many different tissues. As an example, until very recently all textbooks maintained that the nerve cells - neurons - in the brain could not be replaced. You began mature life with a certain number of neurons which steadily decreased as you aged. It is now clear (from work in SRs own lab amongst others) that this isn't true; new neurons are steadily being born throughout life, and especially as a result of new experience and learning. However, it is with embryonic stem cells that we are mainly concerned here.

Stem cells can be maintained in vitro, where they will divide and multiply. Indeed, even in vitro they can be pursuaded to grow miniature versions of the organ into which they would in real life develop. There is a ready source of such cells, derived from aborted human foetuses. And of course, they have the potential to be genetically manipulated. So could they not be used as a vehicle for therapeutic intervention to do what could not be done by somatic gene therapy? This would require an experimental programme of research on stem cells obtained from aborted human foetuses, and such experimentation was explicitly banned in Europe, the UK and, for Federal funding in the US. It was this ban that is intended to be lifted by the recent British legislation, making the UK the first and so far only country in the world to

legalise such research (barring the rather large loophole for non-Federally funded work in the US).

So what might stem cells be used for? The press has made much of the possibility of using them to grow 'spare parts' - skin, muscle, heart or kidneys. Stem cells have also been proposed as a way of treating a variety of neurological disorders, including stroke, spinal injury and Alzheimer's disease. Stem cells could, it has been proposed, rectify macular degeneration, glaucoma, retinal detachment and diabetic retinopathy.

To avoid the problems of tissue rejection such cells would require to be either taken directly from the individual concerned - perhaps by finding ways of harvesting biopsied adult stem cells from his or her own tissue – or - and this has been the macabre speculation - from a specially grown clone. If it were required, such stem cells could presumably be genetically engineered to rectify specific genetic malfunctions. However a host of serious biological problems remain to be overcome - for instance how to control the behaviour of an embryonic cell in an adult environment. After all adult stem cells exist but their activities are clearly powerfully regulated by a host of cellular mechanisms. Just how this regulation is achieved is now one of the major theoretical and practical questions in developmental genetics. As will become apparent shortly, this has proved to be a very serious technical problem.

But before turning to that it is important to spell out the ethical problems associated with proceeding with stem cell research. If we accept that it is necessary to draw a clear line in the sand over which research and therapeutic intervention must not cross - and most of us do insist that this is the case - then where is it to be drawn? Cloning an entire human being - as proposed in the extraordinary circus convened in Rome a couple of weeks ago by the showman-like Dr Antinori and his US and Israeli partners - is for most of us entirely unacceptable, as it implies the use of a human as a means rather than an end - even were it technically possible and safe. And of course such gung-ho technophilia completely ignores the social context in which such a cloned human would be born and grow. The pioneers of mammalian cloning at Roslin have already made it quite clear that there are severe technical as well as overwhelming moral reasons not to go down this line (this will be discusses in more depth). So the danger implicit in permitting stem cell research is that it is yet another step towards crossing that line in the sand, a weakening of the moral resolve which has hitherto prevented it, and a capitulation to the pressures of the biomedical research community and the pharmaceutical companies. This is part of the debate we were planning between the two Roses for this lecture, but which now has to be discussed in Hilary's enforced absence.

However, events over the past few weeks have also sharpened the biological doubts about the potential use of stem cells. The case in point is that for which there has hitherto been the strongest case for their use and evidence of effectiveness. This is Parkinson's disease. As many of you will know, Parkinson's is a common degenerative neurological disorder. Over age 65, around one in every hundred people suffer from Parkinson's. Sufferers begin to experience uncontrollable tremors as they try to reach for or grasp objects; as the condition develops, so also people with the disorder become increasingly depressed. There are multiple risk factors associated with the disease, but all culminate in the death of clusters of neurons deep in the brain (in a region called the basal ganglia). It is these cells who normal function involve communication with the cerebellum - a big mass of tissue at the back of the head - which amongst other things regulates motor coordination. The basal ganglion cells communicate with the cerebellum by way of an important neurotransmitter called dopamine, and in Parkinson's disease, as the cells die dopamine production diminishes or ceases. So treatment for Parkinson's since the 1960s has involved a drug called L-Dopa - a precursor molecule to dopamine which can be taken up into the brain and enzymically converted, so as in some measure to replace the endogenously produced transmitter.

When it was first introduced, l-Dopa was seen as a wonder drug. Its effects are dramatically described in the first of Oliver Sacks' popular books - Awakenings. On the drug, people recovered muscular coordination otherwise lost for ever. But L-Dopa has also proved problematic. Its effects are temporary, and also long term use of the drug has produced some of the symptoms associated with overproduction of dopamine – including schizophrenia- like episodes and hallucinations - also vividly described by Sacks.

Sensationally, some thirty years ago a group of Mexican researchers claimed that they could alleviate the symptoms of Parkinsons by transplanting embryonic brain tissue directly into the basal ganglia. The experiments were widely condemned as unethical, inadequately controlled and with dubious outcome. However, the way was opened for researchers in the UK, Sweden, France and of course the US to follow the work up. We seem to remember the one time leader of the Liberal Party, Jeremy Thorpe, volunteering for such treatment, but until the end of the 1980s the research - at least as far as it has been controlled in more ethically legally regulated contexts - focussed on 'animal models.' To everyone's surprise, the brain transplants seemed to survive, even to put out new processes and make new synaptic connections with other neurons. Were they restoring function by replacing the old dead or dying cells? Or were they merely functioning as little minipumps, pouring out dopamine? At least one researcher argued that the therapeutic effect could be mimicked simply by making a lesion in the animal's brain and closing the wound without any insertion of brain tissue at all!

With the advent of the new genetic engineering techniques in the early 1990s some researchers turned away from transplants and tried to engineer viruses (plasmids) containing replacement DNA that could be injected directly into the brain. Again, the technique seemed promising, but not sufficiently so to attempt to work with humans. Just last year, experiments with rhesus monkeys suggested that a viral (lentiviral) delivery of a neural growth factor (GDNF) into the brain could alleviate some of the symptoms of experimental Parkinsson's. A further approach was to take tissue from elsewhere in the patient's body (the adrenals) and transplant that into the brain. However, since 1987 the use of foetal stem cells in the treatment of Parkinson's has been continuing on an experimental basis in Europe and the US. About 250 people have so far been treated this way. Some six to eight embryos are required for each treatment, to yield about 200,000 neurons, which can beinjected in a sort of slurry directly into the patient's brain. The work has been pioneered in Europe by Anders Bjorklund in Lund, in Sweden, in conjunction with researchers in Cambridge and at the Hammersmith Hospital in London. The team forecasts that if they are allowed to grow the stem cells in vitro before using them, they could manage with fewer embryos to begin with. Whether this would resolve the ethical problem is however another matter.

However, all this techno-optimism was brought to a crashing halt in the middle of last month, when the results of the first full clinical trial using foetal material were published, involving some 40 patients. The therapy produced no benefit for patients over 60, and whilst some of the younger patients did improve, 15% were actually worse off, with persistent finger chewing, uncontrolled jerky movements and loss of intellectual function. The problem, simply, seems to be one of control. The embryonic cells grow uncontrollably; too much dopamine is produced, and the consequences seem irreversible. The stem cell researchers argue that if carefully harvested and cultured stem cells are used, the problems can be circumvented, but up till now this is no more than whistling in the wind.

The lesson is that there are no miracle cures. Like cystic fibrosis for gene therapy, Parkinson's for foetal and stem cell transplants are 'best cases' - the most likely ones to try for because of what is known about the biochemical causes of the condition, tissue access and other factors. Stacked up behind Parkinson's, enthusiasts claim, will be Alzheimer's and stroke. Yet these, because of the nature of the brain damage that results, are much less amenable to the stem cell approach.

So should the research continue? Those opposed say no: the possible eventual good is far outweighed by the present ethical damage. Far better to continue to work on new drugs, or to explore the possible use of adult stem cells, derived presumably from the person suffering from the disease. Those in favour see no great ethical line being crossed - and the potential benefits are great, granted there is always going to be a continuing supply of aborted foetuses anyhow. But then, those in favour of any new technological development would say that, wouldn't they. With Dr Antinori and his crew hovering in the wings, offering their march to the glory of being the first in the race to clone, and devil take law, ethics, scientific caution or hippocratic oaths, we shouldn't be too optimistic.

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