



Stem cell research and animal research in dementia

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Introduction

Alzheimer's disease and other types of dementia are now a key focus for medical research worldwide. Researchers are investigating how dementia affects the normal functioning of the brain and looking for new ways to treat it.

Often, dementia research involves the use of animals. There is now also growing interest in the treatment potential of stem cells derived from human embryos. Both these types of research raise ethical questions and are controversial.

Some people feel very strongly one way or the other about stem cell or animal research. Many more feel they lack the information to come to an informed opinion. This information sheet gives an explanation of each type of research, as it is used in dementia, and looks at the issues.

Stem cell research

What are stem cells?

Living creatures are made up of many cells, which form the body and all its organs. Humans have about 300 different types of cell, each specialised for a particular job: for example, brain cells, blood cells, skin cells and muscle cells. Although they all contain the full genetic code, different parts of it are switched on and off in different types of cell; so, for example, liver cells can't do the job of bone cells. Within the brain, there are many kinds of cell which do specialised jobs.

Stem cells are cells which have the potential to produce different types of specialist cells when they divide, including all the specialised types of brain cell.

Types of stem cell

Not all stem cells are the same. Some stem cells can make any kind of cell in the body. These are called 'pluripotent' stem cells, and are found in early embryos. They are the starting point for every kind of cell in the body. These embryonic stem cells can be kept for many years in a laboratory, because they can keep dividing, making more stem cells which are also pluripotent. They are potentially the most useful type of stem cell.

Other stem cells can make a limited range of types of cell. These are called 'multipotent' stem cells. Adults and children have many different kinds of multipotent cell in different parts of the body. They form new cells of different types as they are needed. For example, stem cells in bone marrow make red and white blood cells, and stem cells in other parts of the body make new cells to replace damaged or dying cells. Unlike embryonic stem cells, however, they can each only make a limited number of types of specialised cell, and they will not keep multiplying themselves in the laboratory.

Where do human stem cells for research come from?

There are three main sources of human stem cells: early embryos, aborted foetuses and adult tissues.

Sources of pluripotent cells

Researchers can get pluripotent cells in three ways.

- **Spare embryos:** Stem cells can be extracted from spare embryos donated by couples having fertility treatment. The cells are extracted about 5-7 days after fertilisation. Extracting the cells destroys the embryo (which, because it was not needed for the fertility treatment, would have been destroyed anyway).

- **Foetal material:** Stem cells can be taken from certain parts of a foetus after a pregnancy is terminated between 5 and 9 weeks. These are the 'foetal germ cells' – the parts which would have developed into ovaries or testicles.
- **Therapeutic cloning** (also known as 'cell nuclear replacement', or 'nuclear transplantation'): In therapeutic cloning the genetic material (nucleus) from a single cell from an individual is put into an unfertilised egg donated by someone else, replacing its own nucleus. The egg is made to divide as if it had been fertilised by a sperm. This creates an early embryo which has the genetic make-up of the individual. Stem cells can then be extracted from the embryo, which is destroyed in the process and so could not develop into a person¹. These stem cells can be used for research and in the future - in theory - for treatment.

Sources of multipotent cells

Researchers can get multipotent cells from several sources. These are some examples.

- **Umbilical cord blood**, taken after the birth of a baby, is a good source of blood stem cells.
- **Bone marrow** stem cells from adult donors are already used for transplants for patients with leukaemia.
- **Other body tissues**, including the brain, contain stem cells. Brain stem cells from aborted foetuses are being studied as a possible treatment for Parkinson's disease.

However, sorting out the stem cells from all the other kinds of cells in the tissue is very difficult.

¹ A human embryo created in this way cannot be allowed to develop further, as this would be 'reproductive cloning', which is how Dolly the sheep was produced. Reproductive cloning of humans is forbidden by law.

Stem cells in dementia research

When someone has dementia, brain cells are damaged and killed, but not replaced.

Some potential aims of stem cell research into dementia treatment could be:

- to get the stem cells already naturally present in the brain to replace the cells destroyed by dementia
- to put new stem cells into the brain and get them to replace the cells destroyed by dementia.

Stem cells could also help dementia research in other ways, for example:

- using therapeutic cloning to make a supply of embryonic stem cells with the genetic makeup of diseases such as hereditary forms of dementia, so as to study the genetics and biochemistry of the disease
- using stem cells to produce large amounts of cells (for example, brain cells) which are hard to obtain in other ways, in order to test drugs.

However, there are many obstacles which researchers would first have to overcome. Simply transplanting stem cells into the brain is unlikely to be the answer. Stem cell research is at a very early stage, and there is a lot of vital information that researchers do not yet know. For example, more basic research, most of it involving animals, is needed to understand:

- how to get a pure sample of stem cells out of the mixture of cell types in an organ such as a brain
- whether multipotent stem cells, which are limited to forming only a few types of new cell, can be persuaded to become pluripotent, with full potential to make every kind of cell
- how to persuade stem cells to make the kind of new cells that are need
- how to persuade new stem cells to go to the areas where they are needed – in most

kinds of dementia, the damage in the brain is not limited to one area

- how to get the new cells to work with other brain cells
- how to make sure that stem cells don't keep on making too many cells, causing cancer.

There are also potential dangers, such as accidentally using stem cells which are infected with a virus or prion². If an infected stem cell was used to create more stem cells, many patients could potentially be infected. A new European directive means that by April 2006, extra safeguards will be in place to try to prevent this possibility.

There are some early hopeful results. In Parkinson's disease, the damage is mainly limited to one specific area of the brain, where cells that produce a chemical called dopamine die. Some patients have been treated with brain implants of foetal brain cells which produce dopamine, with mixed results. However, these are not stem cells and do not divide after they are transplanted. In studies on animals bred to have Parkinson-type symptoms, stem cells transplanted into the animal's brain have moved to different areas and produced a range of cells, including ones which make dopamine. But there is much more work to be done before this might be a treatment suitable for humans.

In most forms of dementia the damage in the brain is more widespread, so it is not guaranteed that success with this method for Parkinson's disease would lead to benefit for people with dementia.

Regulation of stem cell research

In the UK, stem cell research is carefully regulated by law.³ Any research involving

² Prions are proteins which can cause infectious diseases such as Creutzfeldt Jacob disease.

³ Human Fertilisation & Embryology Act 1990: www.legislation.hmso.gov.uk/acts/acts1990/Ukpga_1990037_en_1.htm, Human Reproductive Cloning Act 2001: www.hmso.gov.uk/acts/acts2001/20010023.htm

stem cells must be licensed by the Human Fertilisation and Embryology Authority (HFEA). For a study to be licensed, they must be satisfied that creation and/or use of embryos is necessary and the work could not be carried out in another way. The research must be needed for one of a limited list of specified purposes, which includes:

- to increase knowledge about serious disease
- to enable any such knowledge to be applied in developing treatment for serious disease.

It is against the law to use an embryo more than 14 days after conception. This limit was chosen because it is when the embryo starts to show the primitive beginnings of a nervous system. It is also illegal to place a human embryo in an animal or an animal embryo in a woman.

A new EU directive⁴ means that from April 2006, there will be extra safeguards on all use of human tissues and cells, including stem cells, to ensure their quality and safety. The new rules cover selection of donors, testing the starting material for producing quantities of stem cells, tracking cells from donor to recipient, and reporting of adverse events, for example if someone developed an illness after receiving a stem cell transplant. The source of all material will have to be traceable.

What are the ethical issues?

The rights of the embryo

Some 'pro-life' and religious groups see the embryo as being fully human from the moment of conception, and thus having the same rights as a person. They see using an early embryo for research as no different to killing a human being for research, and do not feel that it can be justified, whatever the

potential benefit to others. Other people see early embryos as simply a collection of cells with the potential eventually to become a person, but which can be treated just as we might treat any other human tissues. In between is the view of the embryo as human life to be respected, but not a person with a person's rights. Some people see using spare embryos in research on serious diseases as preferable to simply destroying them.

The law in the UK gives the early embryo special status but allows its use in certain circumstances and with regulation and monitoring.

The severity of the illness

Balanced against the rights that the embryo may be seen as having is the great potential benefit of stem cell research for a very large number of people. There is at present no cure for dementia, along with many other common degenerative diseases. 63,000 people in Scotland have dementia, and current treatments are limited. A House of Lords report into the issue said, 'Stem cell treatments, unlike most conventional drugs treatments, have the potential to become a life-long cure.'⁵

There are many other potential research approaches to dementia. Only with hindsight will we know which approaches lead to successful treatments.

Why not use adult rather than embryonic stem cells?

Most of the ethical issues relate to stem cell research using embryonic or foetal stem cells. Stem cell research using adult stem cells is fairly uncontroversial. For this reason, some people believe that research should focus only on adult stem cells.

⁴ European Directive on Tissues and Cells: <http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:32004L0023:EN:HTML>

⁵ House of Lords, 2002. *Report from the Select Committee Stem Cell Research*. London: The Stationery Office Books. www.parliament.the-stationery-office.co.uk/pa/ld200102/ldselect/ldstem/83/8301.htm

The House of Lords report concluded that research should continue into both adult and embryonic stem cells, for maximum medical benefit. The report said that adult stem cells could potentially be taken from the person being treated, avoiding immune rejection if transplanted. However, this is unlikely to be possible for some conditions, including dementia, where it would require extracting stem cells from the brain. Also, it is difficult to isolate stem cells from other types of cell, and it is not clear how they produce other types of cell, how good they are at doing this when transplanted, how long they might continue to divide in order to replace diseased cells, and how effectively and safely they can be made to produce particular cell types.

The report said that more research is needed on embryonic stem cells, because they are pluripotent and easier to isolate and keep, in order to understand how stem cells produce other types of cells and how this can be controlled. Although much of this work would be on animal embryonic stem cells, it will also be necessary to compare what happens in human embryonic stem cells. The report said that at some point in the future, if it becomes possible to make adult stem cells pluripotent, embryonic stem cells might no longer be needed, but that is not yet the case.

Why not use the embryonic stem cell lines we already have and stop making more?

Because embryonic stem cells keep dividing under laboratory conditions, they can be kept as 'stem cell lines', a kind of library of different kinds of stem cells which researchers can use. Some people believe that this means that existing stem cell lines could be used for research, without the need for collecting more from embryos. In the US, state funding for stem cell research is restricted to existing stem cell lines. However, recent research has shown that these have become contaminated or unhealthy because of the way they are grown in the laboratory. This means it may not be possible to use them for future treatments.

Creating cloned embryos especially for research purposes

Most embryos used for stem cell research are donated by couples having fertility treatment because they are not needed for the treatment. The main use for cloned embryos is likely to be for research, for example to create a supply of cells with a particular disease. In future they could, theoretically, be used for a transplant back into an individual without risk of rejection, because they are a genetic match. However, such treatments may be impractical on a large scale, because so many donated eggs would be needed.

Some people oppose using therapeutic cloning to create embryos especially for research. In 2000, the European Group on Ethics in Science and Technology, which advises the European Commission, said that it was premature to allow cloning of embryos, as research could be done using spare IVF embryos. The House of Lords Select Committee recommended that embryos should not be created specifically for research purposes unless there is a demonstrable and exceptional need which cannot be met by the use of surplus embryos. A Church of Scotland report⁶ points out that although cloning a person is illegal in the UK, developing technology for cloning embryos could make it easier to do so elsewhere.

Animal research

Why are animals used in medical research?

There are many medical research techniques which do not use animals. Some laboratory research uses cells and tissues taken from humans, animals, plants or other organisms. Other research looks at humans, either individually or in groups, to understand how diseases affect them. Some research uses

⁶ Society, Religion and Technology Project, 2004. *Ethical problems with cloned embryo research*. Edinburgh: Church of Scotland

human volunteers, for example to test treatments.

Most researchers say that there is some research which cannot be carried out without using animals. Using animals helps researchers understand how the whole living body works, how it goes wrong and how it is affected by treatments such as drugs or vaccines. Animals are used for work which could not be carried out in the test tube and could not be done on humans. About 10% of medical research involves animals.

In the past, animals were used in research more widely and with less regulation. Many of the treatments and techniques we now take for granted were developed using animals. However, there is now greater concern about the ethics of using them and about the welfare of the animals involved. As a consequence, animal research is now carefully regulated in the UK and elsewhere, and worldwide there is much research going on into developing more techniques to minimise the use of animals.

Animals in dementia research⁷

Primates

Only a very small percentage of animal research uses monkeys. Using other primates such as chimpanzees, orang-utans and gorillas is not permitted. Although other animals are also used to help researchers understand how the brain is organised, monkeys are used because of the relative similarity of monkey and human brains. Other animals do not have the same level of development of brain functions such as memory and cognition. Clearly monkey and human brains are different in many ways, but there are also many things they have in common.

Although monkeys do not appear to get Alzheimer's disease naturally, it is possible to

give them some similar symptoms, such as memory loss and behavioural changes, for example in order to test potential new drug treatments.

Monkeys have also been used to gain understanding which could not be gained from brain scans or from human brains after death. By implanting tiny electrodes, under anaesthetic, researchers can find out about how the brain works and how its systems interconnect at a microscopic level. The roles of different parts of the brain can be studied by damaging very specific brain areas. The monkeys are tested using puzzles and computer screens, usually with food as a reward. This type of information may help in understanding what goes wrong in brain diseases such as dementia.

Transgenic mice

- studying how the genes work in hereditary early onset Alzheimer's disease
- studying the causes and mechanisms of the development of plaques and tangles in the brain, and how this might be slowed down or blocked
- investigation of techniques for earlier diagnosis
- developing potential vaccines for Alzheimer's disease.

Other uses of animals in dementia research

Many advances in research have only been possible because of animal research. For example, some current drug treatments for Alzheimer's disease aim to increase the brain chemical acetylcholine. Its importance was discovered using human brain tissue, but this was only possible because of earlier animal work which showed how acetylcholine was involved with memory.

Smaller animals, such as nematode worms and fruit flies, are used to understand the development and working of the nervous system, because their nervous systems are simpler. For example, nematodes have only about 300 nerve cells, compared with many

⁷ For a more comprehensive description of the uses of animals in dementia research, see www.rds-online.org.uk, which is the source for much of the information given in this section.

billions in the human brain, but they work in a similar way.

Animals are used to test potential new drugs before they are tried out on humans. This is to test basic safety; for example to make sure that the drug does not cause cancer or damage foetuses, and to understand how the body deals with it.

Much stem cell research uses animals, in order to develop a fuller understanding of how stem cells work and how to manipulate them in order to develop potential treatments.

Regulation of animal research

The use of animals in research is strictly controlled in the UK⁸. The law protects all living vertebrates (animals with a backbone) and one species of octopus; but not invertebrates such as fruit flies or worms.

The law covers any scientific procedure which might cause an animal pain, suffering, distress or lasting harm. A procedure is only permitted when its likely benefits outweigh any pain or distress to the animals, and where there are no alternatives. Three separate levels of licence must be in place before any animal research can be carried out:

- the laboratory or research organisation must be licensed to ensure that it is properly run, with suitable animal care facilities, staffing and staff training
- the researcher must be licensed for the techniques and species of animal they can work with and what establishment they can work in
- the research project is licensed based on why the research is important, why it needs to use animals and could not be done another way, what experiments will be done and what has been done to minimise the number of animals used.

There are three principles which are accepted widely by researchers and which are implicit in the law. These are known as the '3Rs':

- **Replacement** of animals by non-animal methods wherever possible
- **Refinement** of all procedures to minimise adverse effects, stress or suffering to the animals
- **Reduction** of numbers to the minimum necessary to obtain valid results where replacement is not possible.

In 2004, the Government set up the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs). Replacement is the Centre's ultimate aim, 'but for so long as the use of animals continues to be necessary, it is essential that every effort is made to minimise their use and improve welfare'.⁹

What are the issues?

Using animals to benefit humans

Opponents of animal research argue that it is unethical to cause animals suffering for the benefit of humans.

Arguments in support of animal research include:

- finding treatments for serious human disease is important enough to justify using animals (although people may feel differently about what diseases count as serious, and some also support animal research for other purposes, such as cosmetics testing, banned in the UK since 1998)
- animals can benefit too – many drugs used by vets were developed for human medicine
- we use animals for our benefit in other ways, such as eating meat.

⁸ Animals (Scientific Procedures) Act 1986:

www.archive.official-documents.co.uk/document/hoc/321/321-xa.htm

⁹ www.nc3rs.org.uk/mission.htm

Using methods which do not involve animals instead

Opponents of animal research say that other methods of research should be used instead, such as experiments using cell cultures and computer modelling.

Researchers say that they use these methods whenever possible, but they still need to use animals as well, following the 3Rs principles. They argue that the brain is too complicated to be able to use a computer model or cell cultures instead. They also say that, for safety reasons, drugs need to be tested on animals before they are tested on human volunteers, although in the future improved techniques may mean that this changes. However, currently, limiting medical research to what can be achieved without using animals would mean some lines of research would not be possible.

Accuracy of animal models

Opponents of animal research point out that Alzheimer's disease and other forms of dementia are human conditions. They say that animal models of these diseases are artificial and will not help to understand the disease processes. They also say that testing drugs in animals does not make sense, because animals and humans can react very differently and what is safe or effective in an animal may not be so in a human. One example of this is an experimental vaccine which successfully cleared Alzheimer's-type plaques in the brains of transgenic mice, but had to be withdrawn after trials with patients showed that some suffered brain inflammation.

Researchers who support animal research say that humans and animals have a great deal in common – for example, mice share more than 90% of our genes – and that most of their basic body structures and processes are the same. Where there are differences, it can help to develop knowledge of how genes and disease work. They say that without animal research, it would not be possible to develop

many potential treatments to the point where it is safe to start testing them on humans.

Kinds of animal

Many of the strongest feelings about animal research are about the use of cats, dogs and monkeys. Some people feel less strongly about using animals such as mice. Invertebrates such as fruit flies and worms cause even less concern. Their use is not regulated in UK law, and the organisations which oppose animal research rarely refer to them.

The Home Office monitors animals used in research (but not smaller animals such as insects and worms). In 2003, 85% of procedures used rodents such as rats or mice, and dogs, cats, horses and monkeys put together came to less than 1%.¹⁰

Further information

Stem cell research

Human Fertilisation & Embryology

Authority - licenses and monitors human embryo research:

www.hfea.gov.uk

Public Health Genetics Unit – aims to provide a link between academic research, clinical practice and the development of policy within the NHS for genetics. Explanation of history of policy and legislation in the UK and Europe relating to stem cell research in the UK:

www.phgu.org.uk/info_database/elsi/stem_cells.html

The Society, Religion and Technology Project, Church of Scotland

– aims to stimulate balanced debate in the public at large and amongst those working within technology. Cloning & stem cells page:

www.srtp.org.uk/cloning.shtml

¹⁰ www.official-documents.co.uk/document/cm62/6291/6291.pdf

SPUC Scotland – Pressure group opposing abortion, believe that no form of human cloning is compatible with human dignity, and no form of human cloning is ethical. Questions and answers on human cloning page:

<http://www.spucscotland.org/education/students/embryoexp/index.html>

Stem Cell Research Foundation (US) – explanation of the science behind the research:

www.stemcellresearchfoundation.org/About/FAQ.htm#StemCells

Scottish Stem Cell Network

Aims to bring together scientists and clinicians in order to improve the rate at which laboratory research translates into therapeutic benefits for patients:

www.sscn.co.uk/Cells-BtoB.aspx

Animal research

Animal Aid – aims to work, by all peaceful means, for an end to animal cruelty. Article arguing against animal research in neurological diseases such as Alzheimer's and Parkinson's diseases:

www.animalaid.org.uk/campaign/vivi/neurology.htm

Association of Medical Research Charities

– represents UK charities that fund medical and health research. Information on the benefits and regulation of animal research:

www.amrc.org.uk/index.asp?id=77

National Anti Vivisection Society –

campaigning against animal experiments since 1875. Incorporates Lord Dowding Fund for Humane Research to support and fund better methods of scientific and medical research which replace the use of animals:

www.navs.org.uk/research/about/

National Centre for the Replacement, Refinement and Reduction of Animals in Research: www.nc3rs.org.uk

RDS - UK organisation representing medical researchers in the public debate about the use of animals in medical research and testing:

www.rds-online.org.uk



Alzheimer Scotland

22 Drumsheugh Gardens, Edinburgh EH3 7RN

Telephone: 0131 243 1453

Fax: 0131 243 1450

Email: alzheimer@alzscot.org

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Find us on the internet at
www.alzscot.org