Cloning

Research Paper 97/43

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The successful cloning of a sheep from a single adult sheep cell has caused controversy. This paper discusses the cloning work, and its medical, agricultural and ethical implications. It describes reactions to the new technology in the UK and abroad.

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I Introduction

The successful cloning of the live sheep, "Dolly", as reported in February 1997, by a team at the Roslin Institute, has caused both fascination and alarm. The DNA for Dolly was extracted from a single adult mammary gland cell and fused with an egg cell from which its own DNA had been removed. This was then cultured and implanted as an embryo into the womb of a surrogate mother sheep. The resulting lamb is to all intents and purposes a genetically identical clone of the sheep which donated its mammary gland DNA. (Some mitochondrial DNA from the recipient cell outside the nucleus was not removed, and so there remains a slight genetic difference.)

This achievement is remarkable in that it is the first time an adult cell has demonstrated the ability to put into effect the whole genetic identity - the genome - of an animal. It used to be thought that once a cell had developed it switched off its ability to regenerate. This new work raises the prospect that we will soon have the technical ability to clone humans.

This paper discusses these events,and their agricultural, medical and ethical implications. It sets out the current legal restrictions on human cloning, and discusses reactions to the new technology in the UK and abroad.

II Sexual reproduction

The basic unit of all living organisms is the cell. Cells contain "cytoplasm" in which are suspended a nucleus, and other structures specialised to carry out particular activities in the cell. The nucleus of each cell contains a set of chromosomes, coiled structures of DNA, which carry the genetic information for that individual in the form of genes.[1] These genes determine growth and characteristics such as hair colour, although they usually interact with the influences of other genes and with the environment to produce their effects.

In humans ordinary cells (somatic cells) carry 23 *pairs* of chromosomes in the nucleus, of these 22 are matching but not identical pairs, and one pair determines sex, (XX=female, XY=male). Egg and sperm cells carry only 23 chromosomes ie. *one* from each pair. These reproductive cells are termed gametes.

The process of sexual reproduction in humans involves fertilisation of an egg cell by a sperm. Fusion of the two gametes produces the new individual. Thus when fusion occurs the resulting offspring carries maternal and paternal chromosomes, giving a full complement of 23 pairs.

There is a far smaller amount of a second type of DNA present in the cytoplasm that surrounds the nucleus, in structures called mitochondria. This *mitochondrial DNA* contains only about 20 genes, (compared to over 70,000 in the DNA of the nucleus) and acts as the "power pack" for the cell itself. Its actions are as yet incompletely understood.

The cell formed by the union of egg and sperm is called the zygote, and has its own individual genetic identity, derived from maternal and paternal genes. Rapid division of this cell then occurs resulting in the developing embryo. In this process of embryonic development the original unspecialised "stem" cells, which have the potential to develop into any of the different types of body cells, (blood, skin, muscle etc.,) become differentiated and able to perform a specific function. As the animal grows its cells divide and specialise by "switching on" certain genes, and "shutting down" others. Unlike plants, from which it is possible to create a whole new "daughter" plant from one cell, in the animal cell this process of differentiation has been thought until now to be irreversible. The cloning of Dolly appears to show that the process is reversible.

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[1] Each gene is a specific sequence of amino acids at a particular location on the DNA, and it carries the instructions for production of a protein.

III Cloning

Cloning is a type of asexual reproduction that results in two genetically identical individuals. There are two types of cloning:

A. Mechanisms of cloning

1. Cloning by division of a newly formed zygote. Here the resulting embryos will be genetically different from the parent cells - they will contain DNA from both parent cells; but they will be genetically identical to each other. This is the mechanism that takes place in nature to form twins.

2. Cloning by nucleus substitution. Here the nucleus from a cell is removed and transferred to another cell whose own nucleus has been removed. The recipient cell and donor nucleus are induced to fuse by means of passing an electric current. The resulting cell starts to divide and forms an embryo which is genetically identical to the donor cell only.

Therefore the recipient cell contributes no nuclear DNA to the new individual. The role of the mitochondrial DNA of the recipient cell in development of the introduced nucleus is not fully understood.

Until recently scientists have achieved only limited results in cloning animals, although the procedure is used commonly in plant breeding. In 1975 John Gurdon et al. transferred nuclei from skin cells of adult frogs into frog cells from which their own nuclei had been removed.[2] Some tadpoles developed, but none went on to become frogs, leaving unanswered the question as to whether once differentiated, an adult nucleus can recreate the entire body.

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[2] Gurdon J B, Laskey R A, and Reeves O R," The developmental capacity of nuclei transplanted from keratinised skin cells of adult frogs." *J.Embryol. Exp. Morph.* 34 93-112 (1975)

B. Cloning work at the Roslin Institute

1. Previous work

The Roslin Institute, Edinburgh, is run by the Biotechnology and Biological Sciences Research Council. Pioneering work on cloning has been taking place here in collaboration with Scottish biotechnology company, PPL Therapeutics. In 1995 a team led by Dr Ian Wilmut succeeded in cloning sheep by nuclear substitution[3]. Here the nuclear material from a nine-day-old embryo was inserted into an emptied immature egg cell. Because it came from such a young embryo the nuclear material was undifferentiated - it had not yet developed into specialised cells, but still had the potential to develop into all the different types of cell that compose an adult creature - skin, brain, liver, kidney etc. Out of 250 attempts, two lambs were born as a result of this work, named Megan and Morag.

2. Dolly

The first successful cloning from an adult cell, and birth of the offspring, a Finn Dorset lamb named Dolly, was reported in *Nature* on 27 February 1997[4]. The DNA that resulted in Dolly came from a (live) adult mammary gland cell of a sheep. The nucleus of this cell was treated chemically in such a way as to make it quiescent (in an inactive phase - it had stopped dividing). The treated donor nucleus was fused with the empty egg cell by bringing them together in vitro and subjecting them to electrical impulses. The key to the success of the technique seems to have been that the division of the donor nucleus's genetic material was slowed down to a rate acceptable to the recipient egg cell.

The recipient cell seems to have been able to reprogramme this previously specialised mammary gland nucleus so that it was able develop as an embryonic cell and "read" the genome (the entire genetic instructions)for the adult sheep.

The embryo thus formed has genes from the donor cell nucleus only - it is genetically identical in every respect with the animal from which the donor nucleus was obtained, and owes nothing genetically to the female egg into which the genetic material was placed, except for the influence of the few genes of the mitochondria. This embryo was then implanted into the uterus of a third sheep, the surrogate mother, and allowed to develop for a natural birth.

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[3] Campbell K H S, McWhir J, Ritchie, W A Wilmut I. "Sheep cloned by nuclear transfer from a cultured cell line" *Nature* 380 64-66 (1996)

[4] I.Wilmut, A E Schnieke, J Mcwhir, A J Kind and K H S Campbell "Viable offspring derived from fetal and adult mammalian cells" *Nature* vol. 385 p812-813 27 February 1997

Wilmut et al. have demonstrated that nuclei from fully differentiated cells are capable of directing the development of an entire organism when placed in the environment of an egg cell, and it is now possible to envisage cloning of adult mammals in a completely asexual fashion.

3. Technical problems

This technique is, of course, in its infancy, and there were 277 failed attempts before the successful birth of Dolly. When a cell divides it goes through several distinct stages and for the technique to succeed it is necessary for the empty egg cell and the nucleus of the donor cell to be at the same stage of division[5], and this is difficult to achieve. Also, the findings suggest that the egg must contain proteins and enzymes (biological catalysts) powerful enough to remodel and repackage a specialised nucleus. It may be that some cells and not others can achieve this - "Brain and muscle cells are probably so specialised that you can't reset their clocks"[6]

In addition to Dolly the latest experiments have produced three lambs by nuclear transfer from the cells of a sheep foetus aborted after 26 days, and four from a nine-day-old embryo. There was a high rate of miscarriages and abnormalities with the technique, which will need to be overcome. The *Nature* report on the work states that "increased prenatal loss has been reported after embryo manipulation or culture of unreconstructed embryos".

Dr Wilmut himself has been careful to avoid the term "cloning" since the small amount of mitochondrial DNA present in the recipient egg cell had not been removed. Therefore Dolly differed slightly from the donor sheep[7].

Commentators have also raised the possibility that Dolly's DNA may have come from a "stem cell", which are readily found in the mammary gland. These cells are relatively undifferentiated precursors of adult cells, and thus are more adaptable.

The issue of ageing will need to be addressed - will genetically cloned animals age more quickly than those bred conventionally? In addition, cells begin to develop specialised functions more quickly in a new human embryo than in a sheep - giving less time for the adult DNA to take charge of the process of development. However, with geneticists world-

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[5] *New Scientist* 1 March 1997
[6] Wilmut ibid
[7] *Science and Technology Committee 5th report session 1996-97 "The cloning of animals from adult cells"* HC 373-1

wide working on these techniques, it must only be a matter of time before such difficulties are overcome, and the techniques refined so that the ability to achieve the same results with human cells will be a scientific reality. Although the use of this technique in humans to produce viable embryos or even people is a theoretical possibility Dr Wilmut told the Science and Technology Committee[8]:

> It is the unanimous view of the group within the Institute and in the company that we would find this sort of work with human embryos offensive. We can see no clinical reason why you would wish to make a copy of a person. We are pleased that it is illegal in this country. We would support wholeheartedly the idea of prohibition in as affective a way as possible.

An additional practical difficulty would be that it would require large numbers of unfertilised eggs, and the co-operation of women as surrogate mothers. Dr Wilmut said, however, that it might be technically feasible to clone a human within a year or two.

4. Funding

The work at Roslin has been funded in part (65%) by a grant from MAFF. The current funding, £252,000[9] will be halved in April 1997, and withdrawn in 1998, as it was funded on the basis of a rolling contract. The withdrawal of the grant so soon after the breakthrough in technology has caused consternation in some quarters. Professor Graham Bulfield, director of the Roslin Institute, said that he had been warned about cuts in November 1996, but was nevertheless shocked and felt that there were long-term applications of the technology in animal breeding that were of direct concern to the ministry: "how are we supposed to get the funding sorted out by April? ...I will move heaven and earth to keep resources in the cloning programme."[10]

MAFF has commented[11] that it had ceased to fund the work because:

> The technique for cloning sheep is established and the funding has achieved its aims. MAFF funds strategic research until the science has been sufficiently developed for the work to be taken forward by industry or for the knowledge gained to be applied in policy formulation. The research on cloning sheep is now ready to be taken forward by industry, in fact PPL (previously Pharmaceutical Products Limited) has already provided some of the funding and will take forward the medical application of the technology.

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[8] ibid
[9] *Guardian* 1 March 1997
[10] ibid
[11] *Science and Technology Committee 5th report session 1996-97 "The cloning of animals from adult cells"* HC 373-1

In fact, PPL Therapeutics deals with only one medical aspect of development of the technology, and alternative industrial funding will need to be obtained. It is a consideration that if government funds are withheld and work proceeds at private laboratories, that the Government may lose both influence and knowledge of future developments.

Reductions in funding could affect work on other projects at the Institute, and could mean enforced redundancies.

The Science and Technology Committee, meeting to review the work at Roslin, and its implications stated that[12]:

> The reduction in MAFF's funding will damage the Roslin Institute, the Science base as a whole, and British industry. **We recommend that it should be reconsidered urgently.**
>
> If MAFF is to act in such a cavalier and blinkered fashion, it should bear the costs of any redundancies arising from the cut in funding at Roslin. **We also recommend that any successor Committee to this Committee or the Agriculture Committee should conduct a full scale inquiry into the ways in which MAFF commissions and uses research and scientific advice.**

C. Further cloning work

Since the announcement of this work, American scientists in Oregon have cloned rhesus monkeys[13]. In contrast to the Roslin cloning, this did not involve use of cells from an adult animal, but the monkeys were cloned by nuclear transfer of DNA from a newly formed embryo. It is, however the first time a species so closely related to man has been replicated by this means. Current attempts to treat genetic diseases such as cystic fibrosis and sickle cell anaemia have been limited to changing the genetic material of body cells, and these "cures" endure only for the lifetimes of the replacement cells. The Oregon achievement will be helpful in the attempt to replace defective genetic material in stem or embryonic cells as primate research provides the closest alternative to studying these techniques in human embryo cells.

Researchers in Denmark and Australia have been using similar techniques in an attempt to clone cows. The Danish work uses donor cells from adult ovarian tissue of freshly slaughtered cows. There may be difficulties with the technique using DNA from a dead

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[12] ibid

[13] Dr Ron Wolf et al. Oregon Regional Primate Research Centre as reported *Washington Post* 2 March 1997 Work not yet published

animal, as the DNA decomposes very quickly. The Australian team is working in collaboration with Genetics Australia,a firm interested in new techniques for animal breeding. Using donor DNA fibroblast cells[14] from foetuses or cells from the ovaries of live cows, they have produced cloned embryos by nuclear transfer which have subsequently been divided again and again to produce almost 500 genetically identical embryos. They have yet to show that these embryos can produce healthy pregnancies. Bernard Harford of Genetics Australia said[15]:

> We are preparing a production process for genetically identical embryos

It is, however, apparent that knowledge of the techniques needed for successful cloning of mammals will advance rapidly, and ethical debate on its applications will need to keep pace.

Many researchers throughout the world who are involved in this type of work maintain that human cloning is not envisaged. Mr Ron James, managing director of PPL Therapeutics, the Scottish biotechnology company which has been involved in this research with the Roslin Institute, and which has patented the technology jointly with the Institute, dismissed fears that it could lead to the cloning of humans. He said[16]:

> Undeniably the work theoretically brings us a step closer, but there are a huge number of steps to go, and we'd all agree that it was unethical. It would also be illegal to transfer a whole set of genes from a human egg.

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[14] relatively undifferentiated connective tissue cells

[15] *New Scientist* 15 March 1997

[16] *Financial Times* 24 February 1997

IV Implications of cloning

A. Possible Benefits of the work

1. Knowledge of cell division and genetic control

The immediate scientific value of this work relates to understanding the effects of cell differentiation - how a "stem cell" becomes altered so that it has a specialised function eg. a skin cell, a blood cell or a brain cell. The work provides additional clues in the general understanding of the controls of cell division , of genetic control, and of the continuity of the genome - the complete genetic identity of the organism. Alterations in the way cells divide are involved in cancerous changes and in the process of ageing. Improvements in our understanding brings us one step closer to prevention and treatment of cancers and to slowing the ageing process.

It is possible also that a fundamental understanding of how to turn on the genes of the neonatal state in an adult organ, such as a failing heart or brain, could lead to ways of regenerating damaged tissue.

If nuclear transfer were to be allowed in humans, it may in the future be possible to help those mothers who have disorders of mitochondrial DNA to have healthy children by transferring their own healthy nuclear DNA into donor eggs with healthy mitochondrial DNA.

2. Agricultural uses

The cloning work was developed initially with the purpose of providing improvements in the farming field. Professor Bulfield has told the Science and Technology Committee of the House of Commons that the technique could have as great an impact on agriculture as the introduction of artificial insemination. It could be used in cattle breeding to bring the level of the general herd up to the standard of the elite breeding populations. It might take ten to twenty years before this is possible. Only an elite ten or fifteen per cent would be kept for breeding. These would be conventionally bred to maintain genetic diversity.

Animals thus produced might be less susceptible to disease, and could have improved fertility or feed conversion. Better feed conversion could result in less nitrogen excretion, which would benefit the environment.

The average yield of the dairy herds could be greatly increased by these methods, and top quality meat produced with much greater predictability.

3. Medicines and treatments

There are many potential practical applications for the pharmaceutical industry already in sight.

Scientists are already able to produce transgenic animals. These animals have been genetically altered to incorporate a gene from another species, which codes for the characteristic of the donor animal. Work at the Roslin Institute[17] has produced a sheep "Tracey", genetically engineered to produce in her milk huge quantities of a human protein (alpha-1-antitrypsin) which can be used to treat cystic fibrosis. PPL Therapeutics, which specialises in the production of therapeutic proteins in the milk of transgenic livestock has said[18]:

> This involves the injection of a human gene into a fertilised livestock embryo. This "conventional" technology is robust but is limited by the following characteristics
>
> 1) Only a small proportion of animals generated carry the new genes (less than 10%)
>
> 2) Of these, most do not express the human gene in milk at commercially acceptable levels
>
> 3) Genes can be added but not removed

By cloning an animal that has been successfully genetically modified, it could now be possible to produce flocks of medicine-making sheep. Another product that could potentially be obtained in this way is human serum albumen (hSA) for burns and other serious injuries. About 600 tonnes of hSA is required world-wide each year and has to be derived from human blood. The new technique will enable human protein products such as these to be derived from the milk of cloned sheep - it costs less to collect a litre of milk from a sheep than a litre of blood from a person and it contains between 10 and 100 times as much protein[19]. In addition, animals could be selected for cloning that have genes favourable to our purpose eg. animals that lack proteins which induce allergic reactions.

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[17] *Biotechnology* vol.6 February 1988 *Gene transfer into a sheep* J Paul Simmons, Ian Wilmut et al

[18] Science and Technology Committee 5th report session 1996-97 *"The cloning of animals from adult cells"* HC 373-i

[19] Financial Times 24 February 1997

When cloning is possible in cows, they too could be factory farmed for pharmaceutical purposes. They could be genetically engineered to produce any number of products, such as Interferon, and with a high milk yield this could prove a very efficient form of producing medicines.

Dr Ian Wilmut of the Roslin Institute has said[20]:

> the new technology will allow transgenic animals to be produced more cheaply. Genetic modification of the donor cells in culture before they are used in nuclear transfer will also allow us to introduce very precise changes in their DNA and open up the possibilities for a range of new products for the treatment of, for example, cancers and inflammation.

Cloning of tissue cells

Cloning of a patient's own healthy tissue cells could produce a ready supply of bone marrow for leukaemia patients, without the problems of rejection. Simon Fishel, embryologist and scientific director of the Nurture Fertility Clinic in Nottingham has said[21]:

> In many ways cloning could offer enormous benefits. You could clone from an adult or a child that is sick to produce embryonic stem cells that could be used to repair that individuals damaged tissues.

Taken one step further, and whole organs could be cloned. Cells from a patient's own healthy kidney could be used to clone a second kidney - again, there would be no problem with rejection, and no desperate hunt for compatible donors, with all the uncomfortable choices between recipients that takes place at the moment.

B. More controversial aspects

This work has inevitably given rise to public debate, ranging from applause and anticipation of advances in medicine to outrage at the manipulation of animals and to concerns that human cloning may become a reality.

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[20] ibid

[21] *New Scientist* 1 March 1997

1. Animal welfare

The rationale behind the development of this work has been to provide farming animals with favourable characteristics, for instance a uniform and predictable supply of cattle with high muscle bulk and low fat would have great commercial advantages.

Some commentators have ethical objections to our use of animals in this way. The Director of the British Union for the Abolition of Vivisection, Mike Baker, has written[22]:

> The production of Dolly, the cloned sheep, is sad evidence of a prevailing attitude that animals are commodities which can be manipulated and mutated to suit our needs.
>
> We don't know how many other sheep embryos did not develop normally, nor do we know if other cloned lambs died at birth, in the course of producing Dolly. And we will have to wait many years before we understand how further generations of cloned sheep will develop; playing with DNA is at best dangerous, and at worst, could be disastrous.

John Habgood, former Archbishop of York, questions why science is going down this route. He considers the driving force behind most of the research to be the agricultural industry[23]:

> Cloning is a means of standardising products, and that is what the industry always wants. ...Nobody with a commercial interest in meat production is likely to turn down an unlimited supply of identical cattle cloned from a prime specimen. ...I cannot see any morally convincing argument why anybody should want to clone a human being, and some good reasons why they should not. All this, however, is of no immediate practical relevance. The real issues concern animal breeding, and the enormous commercial interest in being able to reproduce standardised life forms predictably and on an industrial scale.

Others will view the new technology merely as an extension of animal farming that has been carried out for centuries - stock has always been chosen for specific characteristics and reared with a view to improving quality and productivity.

2. Genetic diversity

There is a recognition that genetic diversity must be maintained. If all our stock are genetically uniform we lose that genetic variation that is important for survival of the species.

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[22] *Guardian* 27 February 1997
[23] *The Observer* 2 March 1997

If a disease sweeps through herd or a flock of animals, those with resistance will survive. If they are all genetically susceptible and identical all will succumb. Naturally, cloned stock will be chosen because of their resistance to disease, but as has become very apparent recently, new diseases are arising all the time. Professor Bulfield, however, has said that cloning could protect biodiversity and rare breeds. He maintains[24]:

> The control of genetic diversity of animal populations is well understood due to the widespread use of artificial insemination and strategies to both incorporate cloning into breeding schemes and maintain animal diversity are feasible

Alternatively, Chris Polge, an animal biotechnologist recently retired from the University of Cambridge, argues that cloning will never become widespread, even in agriculture. "Animal breeding is making progress all the time because of genetic variation. Cloning fixes [the genome] in its present state[25].

The Banner report of December 1994[26] addressed the ethical implications of the emerging technologies of breeding of farm animals. One recommendation dealt with the impact on genetic diversity. The Government responded to the recommendation:

> The Government is already taking action in this area. Industry is already being consulted with a view to implementing the EC Council Regulation on the conservation, characterisation, collection and utilisation of genetic resources in agriculture(1467/94) and the Convention on Biological Diversity, which require the establishment of a register for breeds and population sizes. MAFF is also funding work at the Institute of Zoology to measure diversity between and within breeds. The data from these two initiatives will form the basis of a database. Cryogenic conservation of gametes and embryos will be further discussed with the industry.

Another recommendation of the Banner report[27] was that a standing committee be set up to consider ethical implications of the new technologies in animal breeding. That this recommendation had not been acted upon was raised by Graham Bulfield when he met the Science and Technology Committee. Thus speculation is now taking place in the heat of the moment.

Few doubt that if research in this field continues the enthusiasms of scientists need to be monitored and controlled, as in the field of xenotransplantation - the transfer of animal tissue

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[24] Science and Technology Committee 5th report session 1996-97 *"The cloning of animals from adult cells"* HC 373-1

[25] *New Scientist* 1 March 1997 p5)

[26] *Report of the Committee to consider the ethical implications of emerging technologies in the breeding of farm animals* December 1994

[27] ibid Para 3.34

into humans - where the Government has decided that more research is needed before trials to transplant pig organs into humans can go ahead, because of the fear that animal viruses may be transferred to humans. It has since been reported that pig retroviruses can indeed infect human cells in laboratory conditions and replicate themselves.[28]

There is unease that the "mad scientist" in playing with DNA may somehow produce results that he cannot then control. Joseph Rotblat, the British Biophysicist who won the Nobel Peace Prize in 1995 after campaigning for years against nuclear weapons, said[29]:

> My worry is that other advances in science may result in other means of mass destruction, maybe more readily available than nuclear weapons. Genetic engineering is quite a possible area, because of these dreadful developments that are taking place.

Could it be possible that a gene could be introduced to a population - perhaps giving susceptibility to a disease - that could be used as biological warfare?

3. Cloning humans?

The greatest reaction, however, concerns the possibility that human beings could be cloned. Doctors and scientists have gone on record to deny that the new technology would be used for cloning humans. The scientists at Roslin maintain that human cloning is not envisaged. The Director of the Institute, Professor Graham Bulfield, stated[30] that they would not allow cloning to be used in harmful ways, and especially not in humans. The British Medical Association is "currently opposed to any cloning techniques being used in humans whether for research or treatment".[31]

Press comment following the Roslin announcement has, however, concentrated on the sensational, much to the exclusion of the possible benefits to be seen in the field of medicine. Many find protestations by the scientific community that human cloning would be unethical and illegal strangely unreassuring. There is a widespread concern that once the technology is available there will be inevitable progression to applying this in humans. It will be difficult to resist the power of human curiosity. There will be many who would consider the use of cloning techniques to be ethically acceptable, in some instances, perhaps to produce a child where a male partner in a couple is unable to produce gametes.

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[28] *Nature Medicine* vol 3 March 1997
[29] Independent 26 February 1997
[30] *Independent* 26 February 1997
[31] Science and Technology Committee 5th report session 1996-97 *"The cloning of animals from adult cells"* HC 373-1

Cloning might also be called on to replicate a dead child. The resulting children would be in the same position as identical twins, but it must be remembered that although identical twins carry identical sets of genes, in fact each has his own personality and sense of "self". The resulting child could suffer from the enormous expectations to be the same as the child that died, and the parents doomed to disappointment.

The spectre arises of cloning a human to replicate oneself - drawing parallels with Ira Levin's "The boys from Brazil" in which clones of Hitler are made, of cloning in order to create a genetic elite. Could the technique be used to create humans for use as spare parts? This is seen to be totally unethical.

There is concern that in guarding against the more sensational possibilities arising from this new technique we will fail to take advantage of the possible medical benefits. Ruth Deech, Chairman of the HFE authority, told the Science and Technology Committee that an outright ban on human cloning could stifle research[32]:

> If the [HFE] Act does have to be amended, we should maintain a flexible approach and leave the door open to the potential benefits of this technique.

There is no doubt that cloning technology has arrived to stay. Whatever decisions are taken in the UK, cloning will take place in some parts of the world.

Wide general debate is needed to discuss the moral and ethical implications and the scientific potential of the cloning work. We need to decide if there is a consensus for halting work in this field, for allowing it to continue unlimited, or for allowing it to continue whilst monitoring and controlling its uses. Many possibilities may arise in the future, which will need ethical consideration:

Should there be a moratorium on cloning?

Should it be allowed - for farming purposes?
- to produce medicinal products?

Should it be allowed in humans - for tissue production only (eg. bone marrow)
- for organs for transplant
- for infertility treatments - if so what should be the rules do have the right to replace a child?

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[32] *Nature* vol 386 13 March 1997

V Current UK regulation of human cloning

Legislation which controls the technique of cloning in humans is dealt with under the *Human Fertilisation and Embryology (HFE) Act 1990.* This was framed with the intention of making human cloning illegal, but it appears that the wording of the Act may require amendment if it is to encompass the Roslin technique.

A. Background to the HFE Act - The Warnock Report

A Committee of Enquiry into Human Fertilisation and Embryology was established in July 1982 to examine the social, ethical and legal implications of recent, and potential developments in the field of human assisted reproduction. The first child resulting from the techniques of "in-vitro[33] fertilisation" (IVF) had been born in July 1978, and opened up the horizons of those working in the fields of infertility and embryology. There were also anxieties that the techniques were developing too fast for their implications to be assimilated and assessed by society in general, especially the techniques' potential role in manipulating the early stages of human development.

The Committee of Enquiry into Fertilisation and Embryology was chaired by Dame Mary (now Baroness) Warnock and its Report[34] was subsequently known as the Warnock Report.[35]

The terms of reference of the committee were:

> "To consider recent and potential developments in medicine and science related to human fertilisation and embryology; to consider what policies and safeguards should be applied, including consideration of the social, ethical and legal implications of these developments; and to make recommendations."[36]

A lengthy consultation period followed with the publication in 1986 of the consultation paper *Legislation of Human Infertility Services and Embryo Research*[37] followed by the White Paper *Human Fertilisation and Embryology: a Framework for Legislation*[38], culminating in the HFE Act.

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[33] *In vitro* literally means in glass (in the test tube) as opposed to *in vivo*, in the body.
[34] Cm 9314 1984 *Report of the Committee of Enquiry into Fertilisation and Embryology*
[35] The report was with the addition of an introduction was republished in 1985 as *A Question of Life*
[36] *A Question of Life* Mary Warnock 1985 p 4
[37] CM 46 December 1986
[38] Cm 259 November 1987

B. Human Fertilisation and Embryology Act 1990

This Act has two facets:

1) The Act reforms the lawful grounds for access to abortion.

2) It legislates for the establishment of the *Human Fertilisation and Embryology Authority* (HFE Authority) which took up its statutory duties in August 1991. Its task is to regulate research on human embryos, the storage of gametes and embryos, and the use in treatment of donated gametes (eggs and sperm) and of embryos produced outside the human body. Much of the Authority's work relates to the inspection and licensing of centres carrying out IVF, donor insemination treatment, or embryo research and it aims to ensure that "human embryos are used responsibly and that infertile patients are not exploited at a vulnerable time."[39]

It was hoped that research would lead not only to improved treatments for infertility and miscarriage, but also that the understanding of reproductive physiology could lead to improved contraceptives (perhaps a vaccine), and to a better understanding and treatment for genetic disorders. There was recognition that with the advance in knowledge of human embryology changes in regulation might be necessary. It was said[40]:

> Human fertilisation and embryology are areas of rapid change and continuous advances in our knowledge. When we came to debate the Bill there were many issues on the agenda which were not considered by the Warnock Committee because they had not even been thought of just those few years before. It is wrong to suggest that passing a law - which we fully support - that says that in principal research should be allowed to go ahead within a legislative framework somehow marks the end of the debate. The matter will remain one of public interest and also of controversy.

HFE Authority was therefore required to keep under review information about embryos and any subsequent development of embryos as well as of treatment services and other services prohibited or which require a licence under the Act .

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[39] HFEA 3rd Annual Report 1994

[40] HC Deb 8 May 1990, Harriet Harman speaking in debate of Standing Committee B

1. Prohibitions on cloning

Cloning by replacement of the nucleus from one cell into another cell is illegal under Section 3.(3)(d) the Act which deals with "Activities governed by the Act"[41]:

> *Prohibitions in connections with embryos*
>
> (3)(d) replacing a nucleus of a cell of an embryo with a nucleus taken from a cell of any person, embryo or subsequent development of an embryo.

There is the **possibility of a loophole** here. The technique used to produce Dolly involved placing the nucleus from the donor cell into an *unfertilised egg*, not into another embryo. Because of this it could be argued that Section 3 of the Act leaves a slight uncertainty - it refers to "replacing the nucleus of a cell of an *embryo*.." In any case, the Authority does not allow human cloning attempts. A licence would be required for treatment, and this would not be granted.

The type of cloning which involves the splitting of a newly formed embryo at a very early stage (the type of mechanism which results in identical twins) is forbidden for treatment purposes under the Code of Practice of the Human Fertilisation and Embryology Authority (December 1995) Section 7 Para 7.22:

> Centres must not attempt to produce embryos in vitro by embryo splitting for treatment purposes.

This is backed up by Schedule 2 of the Act which deals with "Activities for which licenses may be granted":

> 1.(3) A licence under this paragraph cannot authorise any activity unless it appears to the Authority to be necessary or desirable for the purpose of providing treatment services.

However, the Authority does have the discretion to grant a licence for research using the cloning technique by splitting of embryos (up until 14 days after fertilisation), so long as there is no intention to use the embryos for treatment (implantation). Research could therefore be allowed with the purpose of studying the development of the early embryo. Research proposals have to be individually scrutinised and no licence could be granted if the embryos were for

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[41] See Appendix for *Activities Governed by the Act*

subsequent implantation. Prohibition of research on human embryo cloning therefore rests on the fact that all research using human embryos has to be licensed by the HFE Authority, which has announced that it will not give licences for this research.

2. Definition of an embryo

There is a further ambiguity regarding the definition of an embryo. An embryo is considered to be the product of fertilisation. When cloning takes place without the process of fertilisation, does this result in an embryo? It could be considered that the passage of the electrical current that initiates the subsequent cell division and development of the new individual is analogous to fertilisation. However, if this analogy is not accepted, the law may need to be amended to give the same protection in law that an embryo has.

The Act's definition of an embryo is as follows[42]

> (a) embryo means a live human embryo where fertilisation is complete, and
>
> (b) references to an embryo include an egg in the process of fertilisation,
>
> and, for this purpose, fertilisation is not complete until the appearance of a two cell zygote.

Dr Wilmut and Professor Bulfield maintain that the Act's definition would not, in scientific terms extend to embryos created by the cloning process:

> "The oocyte is an egg but it has not been fertilised and it never is fertilised because the nucleus is transferred to it."

The Science and Technology Committee report[43]:

> The Human Fertilisation and Embryology Act is constructed around defining what may or may not be done to human *embryos*, and about the circumstances in which gametes can be used in infertility treatment. The core provision is that research on embryos of more than fourteen days is prohibited and research on younger embryos is only permitted if it is licensed by the HFE Authority; there is no restriction on research into human gametes. In this as Mrs Deech [44] said, the definition of "embryo" is crucial. The Department of Health told us its current legal advice indicated that the courts were likely to favour a broad interpretation of the Act. We would

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[42] Section1(1)

[43] Science and Technology Committee 5th report session 1996-97 *"The cloning of animals from adult cells"* HC 373-1

[44] Chairman of the Human Fertilisation and Embryology Authority

welcome this, but it is not clear that such an interpretation would be warranted.

3. Research licences

The details of regulations governing the use of embryos for research purposes is given in the HFE Authority Code of Practice 1995:

> 10.1 All research which involves the creation, keeping or using of human embryos outside the body must be licensed by the Authority[45]. A centre must apply to the authority for each research project.
>
> 10.2 The authority may grant licences for research projects for the following purposes only:
>
> a. to promote advances in the treatment of fertility;
>
> b. to increase knowledge about the causes of congenital disease;
>
> c. to increase knowledge about the causes of miscarriages;
>
> d. to develop more effective techniques of contraception;
>
> e. to develop methods for detecting the presence of the gene or chromosome abnormalities in embryos before implantation.

The Authority cannot grant a licence unless it is satisfied that the use of human embryos is essential for the purposes of the research.

> 10.4 The following activities are prohibited by law:
>
> a. keeping or using an embryo after the appearance of the primitive streak[46], or after 14 days, whichever is the earlier;
>
> b. placing an embryo in a non-human animal;
>
> c. replacing the nucleus of a cell of an embryo with a nucleus taken from the cell of another person, another embryo, or a subsequent development of an embryo;
>
> d. altering the genetic structure of any cell while it forms part of an embryo.
>
> The Authority will not license research projects involving embryo splitting with the intention of increasing the number of embryos for transfer (see above Section 7 Para 7.22).
>
> 10.6 Embryos which have been appropriated for a research project must not be used for any other purposes[47].
>
> 10.7 Centres should refer each research project to a properly constituted ethics committee for approval before applying for a research licence.....

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[45] HFEA Act 1990 s.3(1)

[46] A groove of cells that appears in the embryonic disc at 14-15 days after fertilisation - taken to be the first sign that the embryo will develop

[47] HFE Act 1990 s.15(4)

C. Gene Therapy Advisory Committee (GTAC)

GTAC is a non-statutory body which has three main functions:

a) carrying out case-by-case individual protocols;

b) reviewing more general issues relating to such therapy and

c) providing advice to UK Health Ministers on developments in this field and on their implications

It states in the GTAC first annual report that

> it has been made clear to all those with responsibility for gene therapy research that no study involving human subjects should proceed without prior review by both GTAC and a local research ethics committee.

GTAC have said[48] that they consider that the HFE Act 1990 puts a moratorium on human cloning. However, if the Authority were to consider any changes, GTAC would expect to be consulted.

D. Human Genetics Advisory Commission (HGAC)

The Government has set up the Human Genetics Advisory Commission to provide an overview of the science of human genetics, different aspects of which are dealt with by a variety of committees[49]:

Gene Therapy Advisory Committee
Local Research Ethics Committees
Advisory Committee on Genetic Testing
The Advisory Group on Scientific Advances in Genetics
Medicines Control Agency
Medical Devices Agency and
Nuffield Council on Bioethics.

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[48] personal communication
[49] Third Report Science and Technology Committee Session 1995-96

The President of the Board of Trade announced on 2 December 1996[50]

> The Advisory Commission will be considering the broad social, ethical and/or economic consequences of developments in genetics, for example, in relation to public health, insurance, patents or employment. They will also advise on the ways to build public confidence in the new science.

HGAC's Terms of Reference are;

1) to keep under review scientific progress at the frontiers of human genetics and related fields;

2) to report on issues arising from new developments in human genetics that can be expected to have wider social, ethical and/or economic consequences, for example in relation to public health, insurance, patents and employment;

3) to advise on ways to build public confidence in, and understanding of, the new genetics.

The Advisory commission will report to Ministers periodically; reports will be published. It will establish contact with people from different sectors in the United Kingdom and will keep in touch with public views on human genetics. It will also keep abreast of developments in other countries.[51]

The chairman of the Gene Therapy Advisory Committee will be a member, as will the chairman of the Advisory Committee on Genetic Testing. The Advisory Commission will report to the Industry and Health Ministers.

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[50] HC Deb 2 December 1996 cc. 488-489W

[51] Department of Trade and Industry 27 February 1997

VI Government response to cloning

The newly formed Human Genetics Advisory Commission , chaired by Sir Colin Campbell, met for the first time, coincidentally, immediately after the news of the sheep cloning was released. They reported[52]:

> Members discussed the recent reports about new research on the cloning of sheep. They recognised that cloning of human embryos by nuclear transfer was already expressly forbidden by the Human Fertilisation and Embryology Act 1990. It was decided that the Chairman of HGAC would write to his counterpart on the Human Fertilisation and Embryology Authority to confirm the adequacy of the existing law.

The Science and Technology Minister, Ian Taylor, has said[53]:

> Developments in genetic science will be closely monitored. The reporting of the remarkable breakthrough achieved at the Roslin Institute risked confusion between science and science fiction. That these advances are made in Britain is a testament to our first class scientists and the world's most advanced regulatory framework. I have discussed the regulation of genetic engineering with science ministers from G7 countries and the British system was widely admired.
>
> ....As long as we keep a close eye on genetics and encourage a full and open debate on the new findings, there is much about which to be optimistic. Research should help provide answers to some of the mysteries of biology - how cells specialise, the implications for ageing, and abnormal change in cancers and inflammatory disorders. There is considerable potential for it to enhance the quality of our lives, though applications in medicine and farming will require much further work.

A. Science and Technology Committee

The Science and Technology Committee met on 27 February 1997 and decided to conduct an enquiry into the experiment at Roslin. It wished to examine issues which appeared of current importance, and to place evidence on the record which should be of use to the Human Genetics Advisory Commission in its future deliberations. The points which most concerned the Committee were[54]:

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[52] DTI press release 27 February 1997 "Human Genetics Advisory Commission puts public confidence at the top of its agenda"

[53] Department of Trade and Industry press release P/97/177 27 February 1997

[54] Science and Technology Committee 5th report session 1996-97 *"The cloning of animals from adult cells"* HC 373-1

- the scientific challenge of the work, and the benefits that might flow from it;

- the adequacy of the law relating to cloning and related issues in both animals and humans.

The committee took evidence from Professor Graham Bulfield, Director, and Dr Ian Wilmut, of the Roslin Institute, and Dr Alan Colman, Research Director of PPL Therapeutics. They subsequently met with the Human Fertilisation and Embryology Authority to discuss the legal implications. A report was issued - *"The cloning of animals from adult cells"*[55] which included the following recommendations:

• The Committee believes that work which would create experimental human beings should not be carried out.

• The United Kingdom already has a well developed system for considering the ethical implications of developments in human genetics.

• We need to be certain that our regulatory system is robust enough to prevent human embryos being cloned and implanted in the United Kingdom, and we need to consider the extent to which we are prepared to allow experimental uses of the technique.

• It is clear that the law relating to the cloning of humans by the Roslin method is at best ambiguous, and at worst sufficiently lax not to catch some applications of the technique at all. While Counsel's opinion will clarify the position, it will obviously not be a binding interpretation of the law. It is not satisfactory for issues as momentous as this to be left until they are decided through test cases. We recommend that the Human Fertilisation Act should be amended to ensure that the Roslin technique comes within its scope. Anyone attempting cloning without the Human Fertilisation and Embryology Authority's approval should face criminal charges.

• We recommend the intention of Parliament to ban cloning should be reaffirmed. We believe it would be possible to produce a formula which would effectively ban cloning a human through primary legislation.

The Committee also looked at the regulation of animal experiments. Research using animals in the UK is only permitted if licensed under the *Animals (Scientific Procedures) Act 1986*, which is overseen by the Animal Procedures Committee. This system is intended to ensure that no unnecessary suffering is caused to the animal concerned. In addition the Advisory Committee on Genetic Modification of the DOE/HE and the Advisory Committee on releases into the Environment of the DOE/HE has an interest in work involving genetically modified animals. The Science and Technology Committee recommended:

• We believe that the current practice is basically sound; there is no need for explicit regulation of experiments involving only harvested material which do not require new techniques of genetic modification.

• We recommend that the regime for considering the ethics of genetic modification in humans should be matched by an effective regime for animals.

• We recommend that animal experiments which appear to have major implications for the science of human genetics are drawn to the attention of the Human Genetics Advisory Commission and, if appropriate, the HFE Authority, by other Committees at an early stage.

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[55] ibid

VII International response

A. United States

The announcement of the cloning of "Dolly" brought a rapid response world-wide. President Clinton requested the National Bioethics Advisory Commission to report on the ethical and legal implications within 90 days, and announced a ban on federal funding for "cloning human beings". A Bill was introduced in the Senate to block federal funds for "research with respect to the cloning of an individual". There is concern that hasty legislation to prevent human cloning will stifle research which could provide medical benefits. Vern Ehrlers of the House of Representatives has been asked by the Speaker of the House to draw up broad science policy recommendations for Congress. He has described his Bills to ban federal funding and impose a financial penalty on anyone attempting such work as a pre-emptive move to deflect more drastic congressional efforts to ban all cloning research, including that on animals.[56]

A Ban on government funding, however, leaves the field open for private investors, and much work is being carried out on cloning techniques in the US.

B. Europe

As well as the UK, Spain, Germany, Canada and Denmark have laws against human cloning, as do some individual states in the US. France and Portugal also have very restrictive laws on the use of cloning.[57] There are, however, many countries that do not. Paradoxically it seems that countries whose religious background ensures the firmest attitude to the sanctity of life have the least safeguards. Italy, for example, has no statutory regulation whatsoever.[58] Attempts to introduce rules governing biotechnology, genetics and life have been frustrated by unwillingness to discuss bioethical legislation, leaving a legal vacuum, with little protection of the rights of patients, and an open field for private health institutions to offer any type of intervention that seems appropriate to them. This has led to the use of in vitro fertilisation methods to achieve controversial pregnancies - in 1994 a woman aged 62 became the word's oldest mother.

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[56] *Nature* vol 386 13 March 1997

[57] *Independent* 26 February 1997

[58] *British Medical Journal* 31 August 1996 with reference to European commission report 1996 *Ethics, Law and Practice in Human Embryology*, Professor Linda Neilsen et al.

Professor Martin Johnson, of the Human Fertilisation and Embryology Authority, has said[59]:

> The important thing isn't to raise fears about what might go on [in the UK], but elsewhere. There's a general consensus that cloning people would be negative, but the legal framework isn't unified.

The European Commission has reacted to the Roslin news by requesting an enquiry into the ethical and biotechnological issues arising from this development. The group advising the Commission on these matters is chaired by Noelle Lenoir of France. A Commission spokesman said that this will be a preliminary survey, and the whole issue will be considered in the light of the reports from different advisory groups. In a statement to the EU's Economic and Social Committee, on February 27, Jacques Santer, the Commission President, said[60] that the crisis sparked off by BSE has :

> revealed the need to adopt our decision-making systems to the momentous step taken by science less than a week ago when it succeeded in cloning a mammal.

In November 1996 the Council of Europe, adopted a draft Convention on Human Rights and Biomedicine. The diversity of ethical opinion throughout Europe and difficulty reaching a consensus, has resulted in broad statements. The Convention states that *where the law allows research on embryos in vitro, it shall ensure adequate protection of the embryo.*

The final text takes no account of the amendments demanded by the Council of Europe's Parliamentary Assembly at its last session in September 1996[61]. The Assembly had insisted the text should ban in vitro research on human embryos *except in the interest of their development or for the diagnosis of more serious illnesses.* The Convention bans the storage of embryos for research, but leaves national legislators to decide whether to authorise research on multiple embryos. The convention forbids the *creation* of human embryos for research. Britain, as the only member-state to allow this, is entitled to opt out of this provision when the convention is ratified by the UK parliament.

Germany, Poland and Belgium abstained because the Convention does not impose a total ban on embryo research, and because it allows in some circumstances research on those unable to give their consent, such as children and the mentally handicapped.

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[59] ibid

[60] *europe environment* 395 11 March 1997

[61] *Europe Environment* 498 December 3 1996

The head of the Council of Europe has called for stricter bioethics regulations to prevent any human cloning.

C. UNESCO

The United Nations Education, Scientific and Cultural Organisation is currently working on a *Universal Declaration on the Human Genome and Human Rights*, which is expected to be presented for adoption by the United Nations in 1998. This again is broadly drafted. It states that :

> no research applications should be allowed to prevail over the respect for human dignity and human rights, in particular in the field of biology and genetics.

Several countries have pushed for the document to include a ban on human cloning. The Norwegian Prime Minister, Thorbjoern Jagland told the Norwegian Parliament[62]:

> Norway will support the proposals from Germany regarding an international research ban on cloning of humans....This declaration will be an important step on the road to an international, legally-binding ban.

D. World Health organisation

The World Health Organisation regards the use of cloning to replicate humans as "ethically unacceptable". A statement by the Director-General, Dr Hiroshi Nakajima, said[63] human cloning would violate basic principles governing medically assisted procreation, including

> respect for the dignity of the human being and protection of the security of human genetic material

He emphasised, however, that opposition to human cloning should not lead to an indiscriminate ban on all cloning research which could benefit the fight against cancer and other diseases.

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[62] *Agence France Press International* 12 March 1997
[63] *Financial Times* 12 March 1997

Appendix 1

Human Fertilisation and Embryology Act 1990 - Activities governed by the Act

Prohibitions in connection with embryos.

3. (I) No person shall

(a) bring about the creation of an embryo, or

(b) keep or use an embryo,

except in pursuance of a licence.

(2) No person shall place in a woman-

(a) a live embryo other than a human embryo, or

(b) any live gametes other than human gametes.

(3) A licence cannot authorise-

(a) keeping or using an embryo after the appearance of the primitive streak,

(b) placing an embryo in any animal,

(c) keeping or using an embryo in any circumstances in which regulations prohibit its keeping or use, or

(d) replacing a nucleus of a cell of an embryo with a nucleus taken from a cell of any person, embryo or subsequent development of an embryo.

(4) For the purposes of subsection (3)(a) above, the primitive streak is to be taken to have appeared in an embryo not later than the end of the period of 14 days beginning with the day when the gametes are mixed, not counting any time during which the embryo is stored.

Prohibitions in connection with gametes.

4. (1) No person shall

(a) store any gametes, or

(b) in the course of providing treatment services for any woman, use the sperm of any man unless the services are being provided for the woman and the man together or use the eggs of any other woman, or

(c) mix gametes with the live gametes of any animal, except in pursuance of a licence.

(2) A licence cannot authorise storing or using gametes in any circumstances in which regulations prohibit their storage or use.

(3) No person shall place sperm and eggs in a woman in any circumstances specified in regulations except,in pursuance of a licence.

(4) Regulations made by virtue of subsection (3) above may provide that, in relation to licences only to place sperm and eggs in a woman in such circumstances, sections 12 to 22 of this Act shall have effect with such modifications as may be specified in the regulations.

(5) Activities regulated by this section or section 3 of this Act are referred to in this Act as "activities governed by this Act".

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95/50	The Environment Bill (HL) (Bill 85 1994/95)	12.4.95