Compassion in World Farming Trust

THE GENE AND THE STABLE DOOR:

BIOTECHNOLOGY AND FARM ANIMALS

A report for

Compassion in World Farming Trust

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CIWF TRUST

Advancing farm animal welfare

Cover Photo. Dolly, the first mammal to be cloned from an adult cell, was born at the Roslin Institute in 1996. When she was 5 years old Dolly developed arthritis, unusual for a sheep of her age, which could be a result of cloning.

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GLOSSARY AND ABBREVIATIONS

AAT	alpha-1 antitrypsin
AFRC/BBSRC	UK government agencies for biotechnology research (AFRC no longer exists)
DNA	deoxyribonucleic acid
cell culture	artificial cultivation of living cells (in laboratory)
chromosome	structure in the cell nucleus that carries DNA
embryonic stem cells	embryo cells that have not yet differentiated into specialised cells for different types of body tissue
EU/EC	European Union / European Commission
FAO	United Nations Food and Agriculture Organisation
FDA	United States Food and Drug Administration
gene	a segment of DNA that controls an inheritable trait
genome	total set of genes in each cell of an organism
GH	growth hormone
hDAF	human Decay Accelerating Factor
IVF	*in vitro* fertilisation
microinjection /pronuclear injection	injection insertion of foreign DNA by micropipette into a newly-fertilised egg
mutation	an alteration in a gene
nuclear transfer	removal of nucleus from a cell and insertion into an oocyte from which the nucleus has been removed
oocyte	immature egg cell
recombinant (DNA)	hybrid DNA produced by joining DNA from different sources
retrovirus	a RNA virus which replicates by integrating its DNA into the genome of the infected cell - the integrated viral DNA is a 'provirus'
SCAHAW	EU's Scientific Committee on Animal Health and Animal Welfare
superovulation	inducing ovary to release more than the usual number of oocytes
transgene/ transgenic	new DNA (foreign or altered) introduced into an organism; organism carrying altered or foreign DNA
UKXIRA	United Kingdom Xenotransplantation Interim Regulatory Authority
USDA	United States Department of Agriculture
xenotransplant	transplant of tissue or organ from one species into an animal of another species
zygote	one-cell embryo formed by fusion of oocyte and sperm

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Summary of report and recommendations

1. **During the second half of the 20th century, biotechnology gave us unprecedented control over farm animals' reproduction, their lives and their welfare. The understanding of how living organisms work that has been achieved by biological science has undoubted potential for good. But there are very serious concerns about the unrestricted application of the power of biotechnology to farm animal production.**

- Farm animal biotechnology is leading to ever greater intensification of our use of farm animals, for an ever wider range of purposes. This is at a time when consumers, farmers and policymakers agree that a move away from intensive farming towards high-welfare sustainable animal farming is essential
- GM and cloning experiments on farm animals have caused and are causing immense suffering and wastage of animals' lives. Much of this is likely to be going on behind the closed doors of the international biotechnology companies
- Many of the large-scale commercial uses foreseen for farm animal genetic engineering and cloning, such as increased productivity, rapid multiplication of high-yielding animals, pharmaceutical or industrial protein production and production of transgenic organs for xenotransplantation, are very likely to damage animal health and genetic diversity and/or deprive the animals of a natural way of life
- Farm animal genetic engineering and cloning, both in experimentation and possible commercial use, raise a number of risks to the environment and human health

2. **There is a serious danger that genetic engineering and cloning will be used to continue our existing farm animal selective breeding policies, which aim for greater production and for cost-cutting. Selective breeding has already caused serious health and welfare problems:**

- Broiler (meat) chickens have been bred to grow so fast that they frequently suffer from painful lameness and 2% die from heart failure at the age of a few weeks [1]
- Dairy cows that are bred for high milk yield suffer from lameness, painful mastitis and decreased fertility [2]
- 'Double-muscled' beef cattle bred for increased meat yield suffer from difficulty in calving, leading to multiple Caesarean sections, and from stress [3]

3. **Genetic engineering of farm animals is a radical departure from conventional selective breeding. Alterations can be made to animals' DNA that could never occur in nature. Human growth hormone genes have been inserted into both fish and pigs. The effect of the inserted gene is often unknown and is usually damaging to the animal. Because of this, few genetically engineered embryos develop properly:**

- Only 1% of injected embryos develop into transgenic animals [4]
- Only 10% of liveborn animals in genetic engineering experiments actually carry the new gene[5] and even fewer of them express it (i.e. produce the new protein)
- 40-50% of transgenic pigs fail to transmit the gene effectively to their offspring [6]

4. **Genetic engineering and cloning are very far from natural breeding methods. They can only be carried out by means of invasive and stressful procedures on large numbers of breeding animals which are used as egg or embryo 'donors' or surrogate mothers. These procedures include females being given progesterone, follicle stimulating hormone, follicle releasing hormone, anaesthetics, antibiotics and surgery for removal and insertion of eggs and embryos. Young female transgenic animals may be hormonally induced to lactate several months before puberty, to check whether they are expressing the transgenic protein in their milk**

- The Royal Society says that surgical implantation of embryos "can cause post-operative pain, super-ovulation can cause discomfort... 'donor' female animals are mated when very young, and this can be stressful" [4]
- The Farm Animal Welfare Council says of live sheep used in cloning procedures, "The accrued stress to these animals of a surgical procedure with recovery, followed by killing, is not insignificant" [7]

5. **Genetic engineering and cloning experiments involve large-scale wastage of animals' lives. Because of the hit-and-miss nature of genetic engineering and cloning, large numbers of mostly female animals are used (and often killed) to produce a few healthy offspring.**

- 51 sheep are needed to produce 1 transgenic lamb by pronuclear injection, according to an industry analyst8. In a normal lowland sheep flock, 51 ewes would rear 80 healthy lambs.
- 10 surrogate mother sows carrying 586 embryos were needed to produce just 5 cloned piglets, in an experiment by a leading cloning company in 2000[9]. Ten normal sows would rear 100 healthy piglets
- 227 adult sheep were used to produce just 3 surviving cloned transgenic lambs in an experiment on 'gene-targeting' in 2000[10]. 227 ewes would normally raise 350 healthy lambs.

6. **Scientific understanding of how inserted genes are integrated and expressed in farm animal genomes is very inadequate. The inserted genes can be expressed in the wrong part of the animal, at the wrong time. When scientists put extra growth hormones into farm animals, this has often led to excessive growth rates and abnormalities:**

- Most growth hormone experiments on pigs have shown "GH constitutively expressed...in sufficient amounts to have a number of deleterious side effects including lameness and infertility", according to Australian animal breeding experts[11]
- In an experiment on sheep, "the transgenic animals were characterised by a very high basal expression of the gene, resulting in severe acromegaly [enlarged bones] in the founder animals, all of which died before one year of age" [12]
- Transgenic fast-growing sheep typically had liver and kidneys twice the normal size, ovaries and pancreas three times normal size and heart and uterus 28% and 37% larger than normal respectively [12]
- In an experiment to control growth hormone expression in pigs, 8 out of 88 transgenic piglets had high levels of growth hormone expressed in all parts of their bodies and were euthanased [11]

- When growth hormone is engineered into salmon, "the endocrine stimulation can be elevated to pathological levels in some cases"[13]. This can result in abnormally enlarged skulls so that the transgenic fish have difficulty in breathing and feeding.

7. **By 2001, cloning had been applied to sheep, cows, goats, pigs and chickens. Biotechnology companies are building up herds of animals which they hope to use for commercial production of food and pharmaceutical or industrial proteins. But there is strong evidence that cloning for reproduction may turn out to be a fatally flawed technology that should not be used. About half of cloned offspring die shortly before or after birth, often because their vital organs or their immune systems fail to develop properly.**

- Only 0.04% to 1.7% of 'reconstructed' (cloned) embryos develop into live offspring, according to a Roslin Institute expert. Fewer than 7.5% of cloned embryos implanted in surrogate mother sheep develop into live offspring [14]
- In a 2000 experiment by a leading cloning company, 11 out of 14 liveborn cloned transgenic lambs died and another 5 lambs were born dead. In total 42 ewes were implanted with 80 cloned transgenic embryos [10]
- In a 2001 experiment to produce cloned 'knockout' sheep, 4 lambs were born live and 4 dead. None of the lambs survived. In total 78 ewes were implanted with a total of 120 cloned transgenic embryos [15]
- In US experiments on cloned transgenic cattle, 3 out of 12 surrogate mother cows died in pregnancy and 5 out of 13 foetuses were stillborn or aborted. 8 calves were liveborn, mostly by Caesarean section. Three had respiratory distress and one of these died from heart and lung failure after 4 days. Another died at 6 weeks with breathing problems and a "grossly dilated" heart [16]
- Two live calves and two oversized aborted foetuses were produced in a German cattle cloning experiment. One calf was euthanased on its second day because of severe malformations of the legs; the foetuses and the dead calf had abnormalities of the kidney and/or liver [17]
- A 2001 US survey of cloned Holstein cattle reported that 6 of 30 calves died shortly after birth, mostly due to placental abnormalities and heart and lung problems. 73% of the pregnant cows aborted. Several calves had high blood pressure and respiratory distress at birth [18]
- Of 7 cloned 'knockout' piglets reported in the US in January 2002, 3 died from breathing or heart problems, another had heart and lung abnormalities, and a total of 6 had abnormalities either of the leg, the eye and ear, or a cleft palate [19]

8. **Apparently healthy cloned animals may have undetected abnormalities. This raises serious questions about the safety of the technology either for the animals themselves or for human use of food, pharmaceuticals or organs derived from them. Cloning experts believe there is a need for a full evaluation of the health of cloned animals.**

- US cloning experts concluded in 2001 that, "even apparently healthy cloned animals can have gene expression abnormalities... that may cause subtle physiological abnormalities which would be difficult to detect" [20]
- There is evidence that cloned animals may age prematurely. Dolly, the cloned sheep, developed arthritis at the age of 5, which is unusual for a sheep of her age and may be a result of cloning [21]

9. There is at present no specific legislation to protect the welfare of cloned and transgenic animals used in farming or industry. Already there is evidence that commercial companies are making genetic changes to animals that could potentially damage their health:

- 'Knock-out' cows are being produced which have their immunoglobulin genes, part of their immune system, replaced with human immunoglobulin genes in order to make human antibodies in cows' milk and blood [22,23]
- Pigs for xenotransplants are being engineered to lack the gene for the α-1,3 galactosyl transferase enzyme, and sheep and cattle are being engineered to lack the prion protein gene, although scientists do not know if these gene deletions could turn out to be damaging, or even lethal, to the animals [24,25]
- Some foreign proteins made in the milk of transgenic farm animals may have the potential to damage the mammary gland or to be toxic to the animals. Biotech companies are engineering animals to produce collagen, a fibrous protein, in their milk [26], which could potentially cause blockages in the udder. Scientists say that high levels of foreign protein production "may adversely affect the mammary secretory gland" [27]
- Cloning companies want to sell clone "families" of 100,000 or more cloned embryos to be used as an alternative to artificial insemination in cattle farming. Unregulated cloning could damage genetic diversity and introduce deleterious genes, with "increased risk of genetic abnormalities, susceptibility to disease and other welfare consequences" [7]
- Scientists are trying to put the mutated myostatin (double-muscling) gene into pigs and sheep, although it is already known to cause calving problems in beef cattle

10. The production and future commercial use of GM and cloned farm animals present a number of regulatory problems and potential risks to humans and the environment:

- Milk, meat, eggs, fish and pharmaceutical products from transgenic or cloned animals, or meat from 'experimental failures', will need to be tested for human safety of the transgene and other chemical residues, and for the health of the cloned or transgenic animals. The possibility of 'pharmed' products made in animals infecting people with viruses or prions (associated with BSE) is a major concern of medicine regulators [28]
- The use of mobile genetic elements, such as viruses, in genetic engineering techniques presents health and environmental risks because genes can recombine and transfer to new hosts. In addition, GM animals could unintentionally be made susceptible to new pathogens that could infect humans or other animals [4]
- Large amounts of potentially hazardous urine and faeces will need to be disposed of from transgenic animal production units. A single transgenic dairy cow could produce 70 litres of contaminated liquid in urine and faeces per day
- Transgenic pigs used for xenotransplants risk transferring Porcine Endogenous Retrovirus (PERV) to people. This could cause a viral epidemic and is a "major concern", according to the UK's xenotransplantation regulatory authority. [29]

Recommendations

- **A moratorium on all experimental and commercial use of GM or cloned farm animals, whether for food production, 'pharming' or xenotransplantation, until scientists have a better understanding of the basic science of genetic engineering and cloning. CIWF Trust believes that this is the only way to halt the current widespread suffering of farm animals subjected to these technologies**
- **Reversal of our present selective breeding practices in favour of breeding for improved animal health and welfare, together with the promotion of dual-purpose and slower-growing breeds**
- **Re-direction of research effort and funding away from farm animal biotechnology and towards commercially acceptable farming and breeding methods that promote animal health and welfare**
- **Provision of public information on the health, management, lifespan and output of GM and cloned farm animals, in the same detail as is available for animals in conventional farming**
- **Establishment of an Animal Welfare Committee, including biotechnology as part of its remit, to advise government on ethical matters regarding all uses of farm animals**
- **Establishment of an Animal Ethics Committee (a) to consider fundamental questions regarding society's relationship with and use of animals, and (b) to promote discussion and debate of such issues**

10 Introduction: biotechnology and farm animal welfare

Biotechnology has already given human beings unprecedented control over farm animals' reproduction, their lives and their welfare. We routinely intervene in the breeding of farm animals by techniques involving the removal, manipulation or insertion of egg, semen or embryo and by the use of DNA analysis in selective breeding programmes. But the biotechnologies that mark a fundamental change in our control of farm animals are genetic engineering and cloning – in other words directly manipulating the genetic material of unborn animals*. For this reason it is vitally important that society and policymakers have a complete picture of how these new technologies do, and could in future, impact on our treatment of farm animals and the future of animal farming.

Compassion in World Farming Trust is not opposed to biotechnology in itself. The understanding of how living organisms function, achieved in the 20th century, has undoubted potential to reduce suffering and improve the quality of life for humans and for domestic animals. But there are very serious concerns about the unrestricted application of the power of biotechnology to farm animals. Often, unfortunately, this seems to be driven by the commercial motives of biotechnology companies, of agribusiness and of some individual scientists, more than by consideration of the real needs of society or the interests of the animals involved. For some scientists, too, it seems that it is more important to "prove that it can be done" than to think out whether it *should* be done or even whether it *needs* to be done. There is a serious danger that the application of genetic engineering and cloning to farm animals is being driven by the same attitudes and pressures that led to animal 'factory farming'.

Farm animals are sentient beings and respect for their welfare must take high priority in any discussion of the ethics and the practice of biotechnology. We believe that up to now there has been inadequate attention given to the welfare of the animals, either by scientists, biotechnology companies or government regulators. The history of selective breeding of other domestic animals unfortunately tells us the same. It was recently reported that 44 out of 188 dog breeds registered with the Kennel Club suffer from inherited eye disorders, often seriously affecting their welfare[30]. In the case of farm animals, breeding aims have usually been to suit them for ever higher production in intensive farming systems, with consequent damage to their health and welfare. It is vital that animal biotechnology is not used to continue these flawed policies.

The decisions we make now about genetic engineering and cloning will have profound effects on the future of our relationship to farm animals and to farming. Farm animal biotechnology is taking us in the wrong direction. It is designed to intensify our use, even exploitation, of farm animals at a time when consumers, farmers and policymakers are increasingly agreed that a move away from intensification towards animal-friendly and sustainable farming is essential. Part of this vision must be that farm animals have the fullest possible life, including exercise, access to the outdoors, the ability to express natural behaviours, normal social

interaction and freedom from pain and stress imposed on them by our husbandry. It means breeding animals for improved health and welfare rather than for higher production. Farm animal biotechnology, now and in the future, must be judged against these standards.

This report aims to give an overview of the current state of farm animal biotechnology and to highlight the implications for animal welfare, human and animal health and safety, and the future of farming. Compassion in World Farming Trust believes that all the evidence shows that genetic engineering and cloning can have no place in the future of sustainable animal husbandry. Up to now these technologies have cost the suffering and the lives of countless farm animals with no benefit to either farmers or consumers. This waste of animals' lives and society's resources is a strong argument for a moratorium on all such experiments and a redirection of scientific resources towards research into animal health and welfare in sustainable agriculture.

** Some experiments have involved injecting DNA into the muscles of young animals (see below Section 5.4.3) but most genetic engineering is done pre-birth.*

Part I: Technology and breeding

20 Modifying farm animals – an overview

Human beings have been changing the physical characteristics of farm animals since the beginning of domestication. All the variation in farm animal breeds that we see today, with visible characteristics such as coat colour, size and shape, have been created artificially by farmers and breeders. In the UK, attempts at 'scientific' farm animal breeding have been ongoing since the 18th century, when Robert Bakewell (1725-1795) famously aimed to put meat on the table of every family in the country.

But even in the early days, breeding experiments could damage animal welfare - Bakewell's pigs, produced by inbreeding, were described as 'rickety' or 'fools' and by the end of the 19th century some of the pigs exhibited at English agricultural shows had been bred to be so obese that they were described as 'animated tubs of lard', which had difficulty standing for the judges and were liable to die by suffocation[31].

It is important to stress that genetic engineering is entirely different from conventional breeding. Alterations to an animal's DNA can be made by biotechnology that would never occur in nature - for example by inserting a gene from a different species. Human growth hormone genes have already been inserted experimentally in both fish and pigs. The effect of the foreign gene on the new host animal is unknown in advance, and is often damaging.

While being a radical departure from previous selective breeding methods, genetic engineering (and also cloning) are in many ways a continuation of the same tradition. For this reason the new technologies raise many of the same concerns for farm animal health and welfare.

2.1 Selective breeding and reproductive technology

Selective breeding means choosing only those animals for breeding that show desired traits, usually related to production. Over the years, farm animals' bodies have been increasingly specialised to fulfil a particular function, such as egg laying or milk or meat production. Selection has been a very important aspect of the intensification of animal farming over the last half century. Even now, breeding companies are making what are described as continuous year-on-year 'genetic improvements' in animals, judged by their productivity. There is now a huge and powerful globalised farm animal breeding industry, and traits and breeds have become international. For some animals, for example chickens and dairy cows, the situation has reached almost the level of monopoly or monoculture. Ninety percent of the world's meat chickens originate from a couple of international breeding companies.

The desired traits that breeders select for most frequently are related to cutting costs for the farmer, by reducing the amount of feed the animals need and the amount of time they take to reproduce or to reach slaughter weight. They include fast growth, efficient feed conversion, early sexual maturity, leanness, high yield of milk or eggs, large number of young, and occasionally disease resistance. Sometimes behavioural traits are selected for unintentionally, such

as 'aggression', high stress levels, or fearfulness.

What consequences does this genetic drive to increased productivity have on the welfare of the animals? Unfortunately, often the consequences have been negative. Selective breeding and reproductive technologies, while they have increased food production, have in many cases been damaging to animal health and welfare.

2.1.1 Artificial insemination, superovulation and embryo transfer

Artificial insemination (AI) is used to spread the genetics of valuable male animals. AI is widely used in cattle farming – for the great majority of dairy herds. AI can be carried out on cows by farmers or stockpeople after training. It involves putting a catheter through the cervix, using a gloved hand in the rectum to manipulate the reproductive tract, and can cause discomfort to cows and even internal injury if the operator is inexperienced. AI is also quite commonly used for pigs (estimates are around 40% in the UK , 60 to 90% in the EU and 60% in North America) and is also used for turkeys because they have been bred to grow so large that they cannot mate naturally.

In sheep farming, breeding ewes are treated with hormones to synchronise oestrus in a flock and to make them produce two, three or four lambs each. Multiple ovulation and embryo transfer (MOET) is a more complex procedure, mainly used for cattle, and is not as common as AI in commercial farming. The object is to produce multiple calves from a high-value cow, using often lower-value cows as surrogate mothers. The production of the high-value embryos is done by injecting the 'donor' cow with gonadotrophins, such as Follicle Stimulating Hormone, to induce multiple ovulation, so that she releases several eggs instead of the normal one egg. She is then inseminated and the embryos are 'flushed out' a week later by inserting a catheter into the uterus. The embryos are either implanted in other cows which have also been hormonally treated to adjust the timing of their oestrus, or they can be frozen and stored. (Removal of eggs from ovaries followed by *in vitro* fertilisation is also sometimes done.) These procedures on cows are painful and require epidural anaesthesia in the EU. Embryo transfer is prohibited under organic farming standards in the UK and the EU[32].

Control of oestrus by administering hormones, superovulation and embryo transfer are all technologies used in conventional farming that are now being taken further in genetic engineering and cloning.

2.1.2 Broiler (meat) chickens

Meat chicken strains have been bred for fast growth, efficient feed conversion and large breast muscles. Selective breeding of broiler chickens for meat production over the last 25 years has halved the time they take to reach slaughter weight (now around 6 weeks). It has also resulted in major health problems and a mortality rate that is 7 times that of laying hens of the same age. According to the EU's Scientific Committee on Animal Health and Animal Welfare (SCAHAW):

"Most of the welfare issues that relate specifically to commercial broiler production are a direct consequence of genetic selection for faster and more efficient production of chicken meat" [33] [Conclusions, 2].

A significant proportion of fast-growing broiler chickens suffer from painful lameness towards the end of their short lives. Around 2% (according to UK

industry figures) die of heart failure at this early age[1]. A 1999 Danish industry study found that 57% of broilers showed evidence of tibial dyschondroplasia, a disorder of bone growth in the leg[34].

Another result of specialised breeding is that the males of egg-laying strains of chicken are not commercially useful. Egg-laying chickens do not have large muscles and males do not lay eggs. Because only fast-growing, heavy-muscled chickens are considered acceptable for meat production, the male chicks of egg-laying breeds are killed at birth.

Fast growing broiler chickens often suffer from lameness

2.1.3 Dairy cows

Dairy cows are selectively bred for ever-increasing milk yield. They are now expected to produce between 30 and 50 litres of milk per day during their 10-month lactation cycle. These high-yielding animals are now recognised to have serious welfare problems because their bodies have been specialised for this one trait. Dairy cows have a high incidence of painful lameness and mastitis[35].

A Danish animal scientist concluded in 1999: "There is also substantial evidence that genetic selection for high milk yields has led to a decline in health, in terms of increased incidence of mastitis and digestive diseases…, more calving problems.. and more lameness… A significantly reduced fertility in dairy cows of high genetic merit [i.e. high-yielding] has also been demonstrated." In the UK and Denmark 90% and 70% respectively of the dairy herd are high-yielding black-and-white breeds. Seventy two out of 217 European dairy breeds, often more robust, are now in danger of extinction[2].

Dairy cow fertility has declined by 12% since the mid-1980s, according to Irish research[36]. Many experts believe that excessive genetic selection for milk yield has damaged the dairy industry and that lower-yielding cows may actually be more profitable to farmers, because they are healthier.

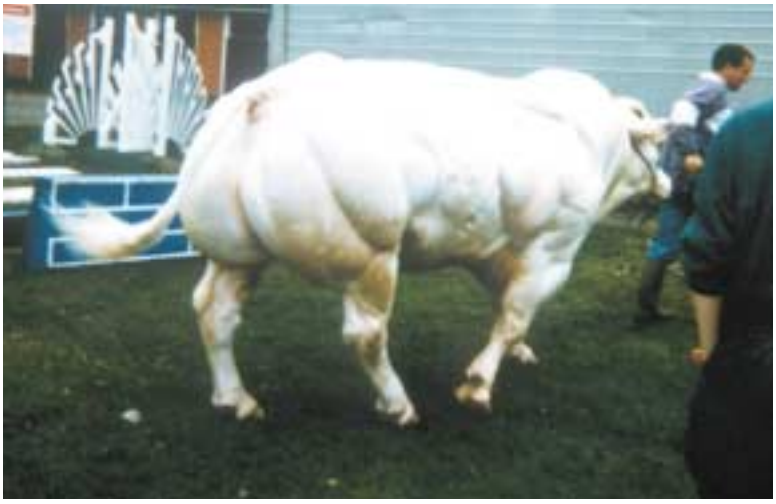
2.1.4 Double-muscled beef cattle

Beef cattle have been selectively bred for large muscles (large meat yield). The EU's SCAHAW says that beef cattle bred for hypermuscularity can suffer from leg disorders, increased calving difficulties and decreased cow longevity[3] [Conclusion 55]. Some breeds, notably the Belgian Blue, have a so-called 'double-muscling' gene, which produces grossly exaggerated muscles and tender meat (See photo below). Double-muscling is known to be caused by a mutation in the myostatin gene, which limits muscle growth. A serious welfare result for homozygous animals (those that have inherited two copies of the mutated gene) is that calving is often difficult. According to the SCAHAW report of 2001 on beef cattle, a French survey of records of herd books showed that 81% of Belgian Blue calvings have to be done by Caesarean section, compared with 4% for

Charolais and 0% for Limousin[3]. These animals also have a higher susceptibility to stress.

The Committee recommends that:

> "Homozygous double-muscled animals have a wide range of problems and should not be used in beef production. The use of heterozygous animals bearing [one copy of] the double muscling gene would still entail welfare problems in the stock of parental homozygous animals"[3] [Recommendation 28].



Belgian Blue cattle carry the 'double-muscling' gene

2.1.5 Pigs

Pigs are selectively bred for faster growth and for leanness. Modern highly selected pigs have been found to be susceptible to stress, sometimes related to a recessive genetic disorder known as Porcine Stress Sydrome (PPS). Pigs that have inherited two copies of the stress gene can suffer sudden death when subjected to stressful situations such as moving or goading, high or low temperature, transport, and slaughterhouses. Pigs with PPS can suddenly develop muscle tremors and twitching, rigidity, rapid breathing and can die within a few minutes. Less badly affected pigs produce excess lactic acid in their muscles due to stress, which gives pale and watery meat, known as Pale Soft Exudative (PSE) meat of low quality. The gene is known as the halothane gene, because pigs with the gene react badly to the anaesthetic halothane, although a DNA test is now available. Some breeders find it useful to produce meat pigs with one copy of the gene (heterozygous pigs) because they are leaner and heavier-muscled. Pig farms can expect 1% stress-related deaths, according to a UK pig expert writing in 1998[37]. This could amount to 120,000 UK pigs dying of stress per year.

Pigs are also selectively bred to make breeding sows very prolific. This can have welfare costs to the sow and piglets, and may even be self-defeating. Commercial sows give birth to, on average, 12 piglets per litter[38], which means that the sow has to be very large and heavy (a quarter of a tonne). Cambridge University Veterinary Department experts believe that large litters result in more small and weak piglets which are at risk of dying or being crushed by the large sow. They suggest that "in the long term, continued selection on the basis of litter size may compromise the overall genetic gain"[39].

2.1 6. Horses.

Artificial insemination and embryo transfer are in use for horses, but these techniques are not currently allowed for breeding racehorses, under racing regulations intended to preserve genetic diversity. But some would like to see biotechnology used to produce champion horses for racing and jumping. Scientists at Cambridge University announced the first foals born from *in vitro* ('test tube') fertilisation in May 2001, seeing this as a first step towards genetic engineering and cloning[40,41]. Colorado State University announced foals born from the transfer of frozen and thawed eggs in July 2001[42].

2.1.7 Sexed semen

Sexed semen is now becoming commercially available for cattle, and is also being developed for pigs. The sexed semen, after processing, contains sperm bearing either the X (female-producing) or the Y (male-producing) chromosome only. In the case of cattle, sexed semen would be delivered frozen in a 'straw' for AI, as is normal semen. In the case of pigs, it is suggested that the separation of female-producing sperm and male-producing sperm in the boar's ejaculate would be done on farm.

Would sexed semen be a welfare benefit? In cattle farming, sexed semen could allow farmers to produce only female dairy calves for replacement milk cows. This could reduce the number of unwanted male dairy calves which are now often shot at birth because farmers do not want to raise them for beef. But sexed semen is also being promoted as a way of speeding up selective breeding, and increasing the uniformity of single-sex herds of cattle, pigs and sheep reared for meat. In the case of dairy cattle, sexed semen is arguably an unnecessary technical fix for a problem caused by over-selective breeding. A better solution would be to use hardier dual-purpose breeds of cattle that could produce both milk and meat. Compassion in World Farming Trust is concerned that sexed semen, as with much reproductive technology, will be aimed at maximising efficiency rather than giving priority to farm animal welfare.

2.2 Genome analysis (Marker Assisted Selection)

DNA technology can be used to analyse the genome of animals with desirable or undesirable traits. Sections of DNA (called 'markers') can be identified in the genome of animals that have particular traits, such as growth, body fat, susceptibility to mastitis, protein content in milk, or resistance to scrapie. Once these markers are identified, the DNA of other animals can be screened at an early age in order to decide whether to breed from them. Animal genome mapping projects such as BOVMAP, PiGMaP and ChickMap already exist[45]. Marker Assisted Selection (MAS) is often seen as a harmless and potentially beneficial use of animal biotechnology. This is indeed possible; MAS could be used to reverse some of the bad results of previous selective breeding, such as 'aggressive' behaviour in laying hens and lameness in meat chickens, and to select for good health.

Unfortunately, there is a danger that breeders and farmers will use the technology to accelerate their drive for faster, leaner growth and higher yield, which is almost certain to damage farm animal welfare. CIWF Trust believes that decisions on breeding objectives should be made with health and welfare as the top priority, rather than with cost-cutting as the over-riding aim.

Patents on GM animals.

The first animal to be patented in Europe, in 1992, was the 'oncomouse', produced at Harvard University. This strain of mouse was genetically engineered to be susceptible to cancer. The patent, which applied to all onco-mammals, except humans, was challenged on grounds of morality by environmental and animal welfare organisations, including CIWF. In 2000, after a 5 year moratorium, the European Patent Office (EPO) confirmed that GM animals can be patented. However, in 2001 the EPO restricted the oncomouse patent to cover only rodents, because "the appeal board felt that it was impossible to assume that the balance between benefit to society and suffering to the mouse could be automatically extended to all types of animals"[43].

Following the oncomouse, patents have been either applied for and granted for numerous genetic manipulation and cloning procedures, and for the trangenic animals themselves. These 'inventions' include using transgenic sheep, cows, goats, pigs, mice, rats, camels and rabbits to produce a variety of pharmaceutical or milk proteins, including human casein and a-lactalbumin for infant feeds; transgenic poultry carrying a bovine growth hormone gene; very fast-growing salmon with inserted growth hormone genes; transgenic animals to produce a foreign polypeptide in their urine; transgenic sheep or goats to produce spider or silkworm silk protein in their wool[27]. Patents have been granted to several companies, including the Roslin Institute and the US biotech companies Advanced Cell Technology and Infigen, for animal cloning by nuclear transfer[44].

Compassion in World Farming Trust is very concerned that the availability of patents on animals will further encourage the breeding of GM and cloned farm animals, in which the animals are very likely to suffer.

2.3 Genetic engineering

Genetic engineering of the DNA of farm animals is being advocated for a number of uses. Some of these are for use in conventional farming and some are for new products. In both cases, genetic engineering is seen as a way of getting 'genetic improvement' in farm animals much faster than by selective breeding. It is also claimed that these genetic changes could be made more 'precisely' (a questionable claim, as we shall see (Section 9)).

Are the aims of genetic engineering valid ones, and how will they affect the animals' welfare? For farming, many of the suggested genetic changes aim for faster or cheaper production, and are unlikely to be of any benefit to the animals. But some suggested genetic changes could in principle have welfare benefits, such as giving animals resistance to diseases that cause them suffering. More commonly, genetic engineering is seen as an efficient and cheap way of producing proteins for human use, in the milk, blood, urine or semen of transgenic animals (a process known as 'pharming'). The proteins could be useful in medical, food or industrial applications. The list below gives an idea of the range of purposes foreseen for genetic engineering of farm animals.

- Increase production from conventional farm animals: to speed up or increase growth (meat, fish), to increase milk yield or wool yield, increase the utilisation of feed by animals' digestive systems, change fertility or produce year-round reproduction
- Breed animals for a speciality food or other product (cows producing human milk proteins or milk with an altered composition of milk proteins)
- Use in experiments to determine the function of animal genes and the effects of heredity and environment, for use in selective breeding

- Breed animals resistant to certain diseases or suited to a certain production environment (scrapie-resistant sheep, heat-resistant or *Salmonella*-resistant poultry, reduce tail-length of sheep, reduce smell of pig faeces)
- 'Pharming'; create animals which produce human or non-human foreign proteins in their milk, for medical or industrial use
- Use of cloning with genetic engineering of the 'donor' cell DNA, as a method of increasing the efficiency of genetic engineering
- Breed pigs with 'humanised' organs for use in xenotransplants (organ or tissue transplants to humans)
- Create animals with genetic diseases for research purposes, referred to as 'animal models' for human diseases (for example, a UK institute has considered producing sheep with cystic fibrosis, a genetic lung disease)

Embryonic stem cells and cloning. Embryonic stem cells (ES cells) are cells that are not already differentiated into specific functions and so have the potential to develop into all tissue types. ES cells can be taken out of very early embryos of mice, genetically engineered and then put back into embryos, where they develop into a number of different cell types. Some of them develop into egg or sperm cells in the grown mouse, which means the animal can produce transgenic offspring. So far, scientists haven't managed to do the same with farm animal ES cells. But cloning of farm animals by nuclear transfer enables scientists to do something similar, by genetically engineering the DNA of a cell taken from one animal and then transferring the engineered DNA to an egg-cell (oocyte) to develop into an embryo. For this reason, cloning is being advocated as the best method of genetic engineering farm animals.

Cells, DNA and proteins. Living organisms are made up of cells, each of them containing a copy of the entire genetic material of the organism. In animal and plant cells, the genetic material (in the form of the DNA molecule) is packaged in chromosomes in the cell nucleus. Genes are sections of DNA that specify the chemical codes for protein molecules that are manufactured by cells. Proteins are large and complex molecules that are central to the functioning of living organisms – either as part of their structure or as part of their biochemistry. If the cell makes a particular protein, the gene for that protein is said to be "expressed". In other words, the gene is functioning in that particular cell. During development and growth, cells become 'differentiated' into different body tissues with specialised functions, for example skin cells or muscle cells. Only a small proportion of the genes are functioning in any one cell at any particular time. The body regulates the switching on and off of genes.

Genetic engineering involves making deliberate alterations to the DNA of an organism by adding, removing or altering genes, for example to make a particular type of tissue produce a particular protein. This may be a foreign protein that the tissue would not naturally produce. A DNA sequence called the 'promoter' gene is inserted along with the gene for the protein, intended to control the expression of the new gene ('transgene') and regulate where, when and how much protein is produced.

2.4 Cloning

The first experiments in farm animal cloning in the UK that resulted in the birth of live young (two lambs called Megan and Morag) were announced in 1996[46]. Megan and Morag were produced from cells taken from very early embryos. Dolly (whose birth was announced in spring of 1997) was the first live clone produced from a cell taken from an adult mammal[47]. Cloning was also seen as a potential route to successful genetic engineering, because the cells used for cloning could be genetically engineered before being fused with an egg-cell. Polly, whose birth was announced at the end of 1997, was cloned from a foetal skin cell after the DNA in the cell had been genetically engineered to include the gene to produce human Factor IX (a blood-clotting protein) in the mammary gland[48].

Scientists are interested in cloning farm animals for a number of reasons, some to do with basic biological research and some to do with commercial production of animals. In animal farming, cloning is being advocated both for reproducing large numbers of high-value animals and also as a method of genetic engineering. Nuclear transfer is seen as the most powerful method of genetic engineering because genes can be altered or disabled ('knocked out') from the DNA of the cell used for cloning, as well as genes being added. A respected researcher told the New Zealand Royal Commission on Genetic Modification in 2001 that by using cloning technology, "there is in principle no limit to the genetic alterations that can be made" to farm animals[49].

The list below summarises the main commercial uses that are envisaged for cloning farm animals:-

- Use cloning to speed up the process of selective breeding or to multiply and sell cloned embryos or young animals of particular high-yielding lines (for example, cloned embryos of high-yielding dairy cows)
- Increase the uniformity of animals for particular market requirement (make all lambs in a flock have the same size, shape and meat quality, for example)
- Use of cloning with genetic engineering of the 'donor' cell DNA, as a method of increasing the efficiency of genetic engineering
- Produce genetically-engineered pigs with 'humanised' organs for use in xenotransplants

This report will concentrate on those uses of genetic engineering and cloning that potentially involve large production herds of animals, such as uses for food, for large-scale pharmaceutical or industrial production and for transgenic organ production.

Embryo transfer for cattle - flushing ova

3.0 3.1 Genetic engineering techniques

3.1.1 Pronuclear injection.

This is the most usual method for farm animal genetic engineering. It involves the 'microinjection' of hundreds of copies of the foreign DNA into recently fertilised eggs. Immediately after fertilisation the one-cell embryo (zygote) has 2 'pronuclei' (one from the sperm and one from the egg) and the new DNA is injected into one or other of them. Microinjection is the usual method for producing transgenic sheep[50] and pigs[6] and has also been tried with chickens[51]. It has a very low success rate of producing transgenic animals, usually only a few percent, with even fewer animals actually expressing the foreign gene. The transgenic animals may turn out to be so-called 'mosaic', that is they have the transgene in some cells but not in all cells. They may have the transgene in some of their egg or sperm cells but not in others. See Diagram 1.

3.1.2 Genetic modification of cells in culture.

This is the method that has been used to produce the large numbers of genetically engineered mice that are used in scientific experiments (see box p 16).

Transgenic farm animals can also be created by genetically engineering body cells (or embryonic or foetal cells) and then using these cells for cloning by nuclear transfer (Section 4.0). The foreign DNA is added to the cells in culture, sometimes by incorporating it in fatty capsules ('liposomes') to help carry it into the cells, or by a number of other methods. Some of the cells incorporate the foreign DNA into their existing DNA (this is called 'transfection' of the cells). Genetically engineering the DNA of cells in culture is potentially more far-reaching than pronuclear injection because it also allows existing genes to be disabled or altered (genes can be 'deleted' by inserting an inactive transgene to replace the normal gene). In the case of chickens, a type of cell called 'primordial germ cells', similar to ES cells, can be used in principle to produce transgenic chickens in a similar way[52].

3.1.3 Retroviral vectors.

In this method, a virus is used as a 'vector' to carry the foreign DNA into the cell that the scientists want to engineer. Viruses consist of genetic material (DNA or RNA) and a protein outer covering ('coat') and they reproduce by infecting a cell and using the cell's machinery to replicate themselves. A method that has caused some concern is the use of retroviruses as 'vectors' to carry the foreign DNA into the cell that is to be 'transfected'. Retroviruses (which include HIV) incorporate their DNA into the genome of the cell they infect.

This method of genetic engineering has been tried experimentally with chickens. Two US companies are reported in 2000 to be using retroviruses (reticuloendotheliosis virus and avian leukosis virus) to put foreign DNA into early chick embryos[53]. Other scientists have used a retroviral vector including part of the Feline Leukemia Virus to put foreign DNA into sheep and pig embryos[27].

Viruses used in genetic engineering are supposed to be made unable to replicate. But there may still be a potential for the wild virus to re-emerge. "The major problem associated with the use of retroviral vectors is

the generation of infectious virus that can be indefinitely transmitted", according to a 1997 review of the technique[54]. During the later 1980s, scientists used avian retroviruses that were capable of replication to put DNA into chickens[52]. It is well known that viruses can mutate and exchange segments of DNA with other organisms (see Section 10.4).

3.1.4 GM sperm

Scientists have tried to genetically engineer the sperm of fish, mice, pigs and chickens. Viruses can be used to carry the DNA into the sperm. One of these is the SV40 virus – a potentially cancer-causing monkey virus that contaminated some polio vaccines in the mid-20th century. Sperm can also be transfected by incubating it with DNA or by using an electric shock to create pores in the cell membrane to let in the DNA ('electroporation')[55]. Genetically engineered chicken sperm has been used successfully to breed transgenic hens, for example by the US company TransXenoGen[56,57]. Another method used for poultry is to irradiate the testicles of a cockerel to destroy the sperm-producing cells and then implant genetically-engineered spermatogonial cells taken from another cockerel[27].

3.2 Producing GM animals

From the welfare point of view, the methods of producing transgenic sheep, cattle and pigs must be seriously questioned. They involve subjecting the animals to invasive, painful and / or stressful procedures, which are not for the benefit of the animals themselves. The UK's Royal Society report in 2001, *The Uses of Genetically Modified Animals*, conceded that surgical implantation of embryos can cause post-operative pain, super-ovulation can cause discomfort and mating donor females when very young can be stressful to them[4].

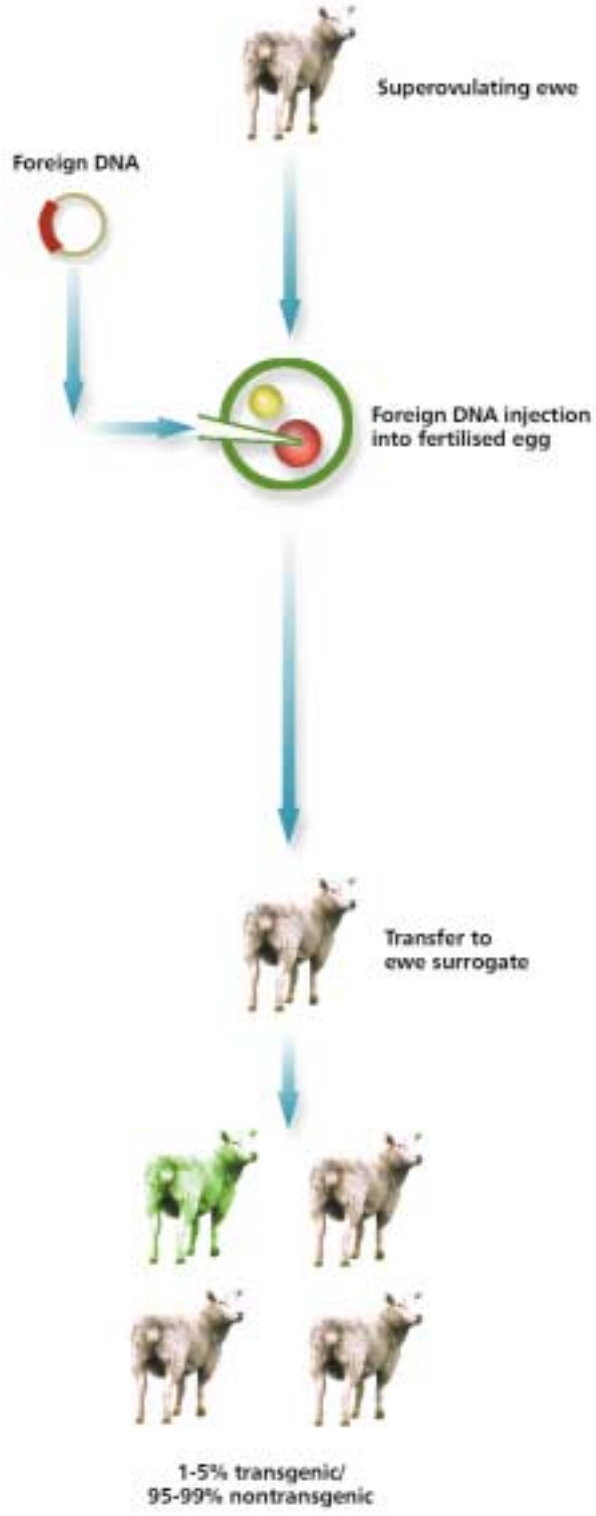


Diagram 1:

Diagram of the main steps in producing a genetically engineered lamb by method of pronuclear injection. In practice most of the injected embryos fail to develop into live offspring and only a small proportion of offspring are transgenic.

The objective of a genetic engineering experiment is usually to produce transgenic animals that express the new gene satisfactorily and that can also pass it on to their offspring. The first animals born that have the new DNA are called 'founder animals' or 'founder transgenics' because in principle they can be bred from to produce more transgenic animals. To use transgenic animals commercially, herd or flocks are needed. A herd or flock can be built up either by conventional breeding of transgenic animals or by more genetic engineering and / or cloning. Although some argue that this process is equivalent to breeding a normal herd or flock, in practice it is very different.

3.2.1 Numbers of animals used

Large numbers of animals are used for the production of relatively few healthy transgenic offspring. An industry estimate in 1999 is that 51 adult sheep are needed to produce one 'founder' transgenic animal, that could be used to start breeding a transgenic flock[8]. This ratio of 51:1 should be compared to the expectation that a commercial flock of normal lowland ewes will rear an average of 1.56 lambs per ewe[58], an equivalent ratio of 0.6:1. Over one thousand genetically engineered sheep were used in experiments in Great Britain in 2000, according to the Home Office[59]. The total number of experiments using GM animals increased nearly 7-fold between 1992 and 1999, to over half a million a year[60].

The following are some typical examples of procedures used to produce GM farm animals.

3.2.2 Sheep

Microinjection is the most usual method of producing transgenic sheep. Ewes are superovulated, artificially inseminated and fertilised eggs are collected. Foreign DNA is injected into the eggs which are then implanted in other ewes. A small percentage of their offspring are transgenic, and attempts are made to breed from them[50].

For superovulation, 'donor' ewes have progesterone-impregnated sponges put in their vaginas for 15 days before AI. To induce superovulation, 5 days before AI they are given twice-daily injections of follicle stimulating hormone. To synchronise ovulation, they are injected with releasing hormone one day before AI. For AI, they are given sedation and local anaesthesic and an antibiotic injection. The next day they are given a general anaesthetic, the uterus is pulled out via an incision and the eggs are flushed out of the oviducts. The foreign DNA is injected into the eggs and the fertilised eggs are put back into ewes. These 'recipient' ewes meanwhile have had a progesterone-impregnated sponge in the vagina for 15 days, removed 2 days before the fertilised eggs or embryos are to be implanted, and they are then injected with follicle stimulating hormone. Under general anaesthetic, the uterus is pulled out via an incision and the embryos are put into it. Because only a few of the offspring have incorporated the foreign DNA, blood samples are taken from the jugular vein and tissue samples are taken from the tail, for example when the lambs are tail-docked. [50]

3.2.3 Pigs

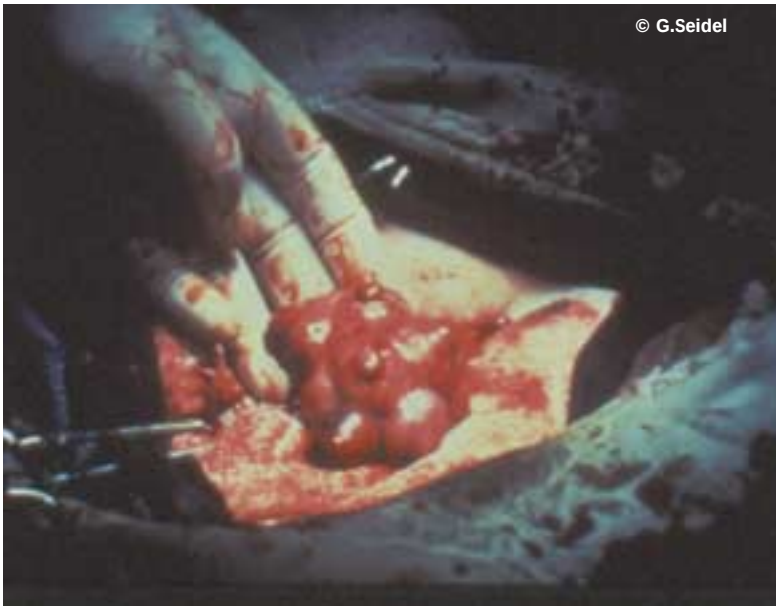
Microinjection is the most common method for producing transgenic pigs. One- or two-cell fertilised eggs (embryos) are removed surgically from sows, injected with foreign DNA and then surgically put back into other sows with synchronised oestrus. The control of oestrus and ovulation is done as with sheep, using an array of hormone injections. Pre-pubertal gilts (young sows), for example, are injected

with pregnant mare serum gonadotropin (PMSG) to induce oestrus. Mature females are fed progestogen to prepare for pregnancy for 14-21 days and pregnant females may be given prostaglandin injections to bring them back to oestrus. The sows are then injected with PMSG and ovulation is induced by injection of human gonadotropin. The sows and gilts are then inseminated, either artificially or by a boar. The eggs are collected by surgery and injected with the foreign DNA. They are then put back into the oviducts of recipient sows. On average, only 0.9% (less than 1%) of gene-injected embryos develop into transgenic pigs. But 40-50% of the transgenic pigs either fail to transmit the gene to their offspring at all, or transmit it to fewer than half of their offspring[6].

3.2.4 Chickens

Chicken genetic engineering does not generally involve invasive procedures being carried out on the hens. One method is to use retroviral vectors to put the foreign DNA into a pronucleus or a one-day embryo[53] (Section 3.1.3). Alternatively a particular type of chicken embryonic cell known as 'primordial germ cells' (PGCs) can be used. The PGCs are taken from an early chicken embryo, 'transfected' with the foreign DNA, and then put back into a slightly later chicken embryo through a window cut in the shell and membrane. In the developing embryo, the PGCs migrate to the gonads and differentiate into either oocytes or spermatozoa. The chicken that develops from this embryo will therefore have transgenic offspring[52,61]. Scientists believe that genetically modified PGCs, like ES cells, can develop into any type of tissue, such as skin and muscle[62].

Superovulated cow ovary



4.0 How farm animals are cloned

4.1 Cloning by nuclear transfer

To clone an individual, a cell, an animal or a plant is usually taken to mean the production of a genetically identical copy or copies. In biology generally, 'cloning' means asexual reproduction, so it also includes propagating plants by cuttings. In the cloning of mammals in farm animal biotechnology, the method used has been 'nuclear transfer'. Nuclear transfer involves inserting the DNA contained in a body cell (or an embryo cell or a foetal cell) into an egg-cell (oocyte) that has had its nucleus removed. The fusion of the nucleus of the inserted cell with the 'enucleated' egg creates a 'reconstructed embryo' which is then implanted in a surrogate mother. The cell that is used for cloning is sometimes genetically engineered in the laboratory before being transferred to the egg-cell. (A small proportion of a cell's DNA (about 3%) is not in the cell nucleus, but is contained in the mitochrondria[63].)

4.2 How Dolly was born

The cell containing Dolly's DNA was taken from a 6-year old ewe killed some years before Dolly was born. To produce Dolly, 'donor' ewes were given hormone injections to stimulate superovulation and their eggs were removed by surgery. Around 690 'reconstructed embryos' were put temporarily into the oviducts of other ewes ('temporary recipients') to incubate. The ewes were then killed and the embryos taken out and checked for normal development. 156 checked embryos were implanted in 61 surrogate mother ewes. Eight lambs were born, of which Dolly was the only one to be a clone of an adult sheep. One lamb died shortly after birth. Two of the lambs were born by caesarean section.[47] Induction of birth or caesarean section are very often needed for the birth of clones (see Section 9.2).

The Farm Animal Welfare Council says of sheep used in cloning procedures, "The accrued stress to these animals of a surgical procedure with recovery, followed by killing, is not insignificant"[7].

In cattle cloning, fewer adult animals are likely to be used, since *in vitro* culture of embryos is often used instead of using cows as temporary recipients (live cows are considerably more costly than sheep). Cow oocytes are often obtained from dead cows at slaughterhouses.

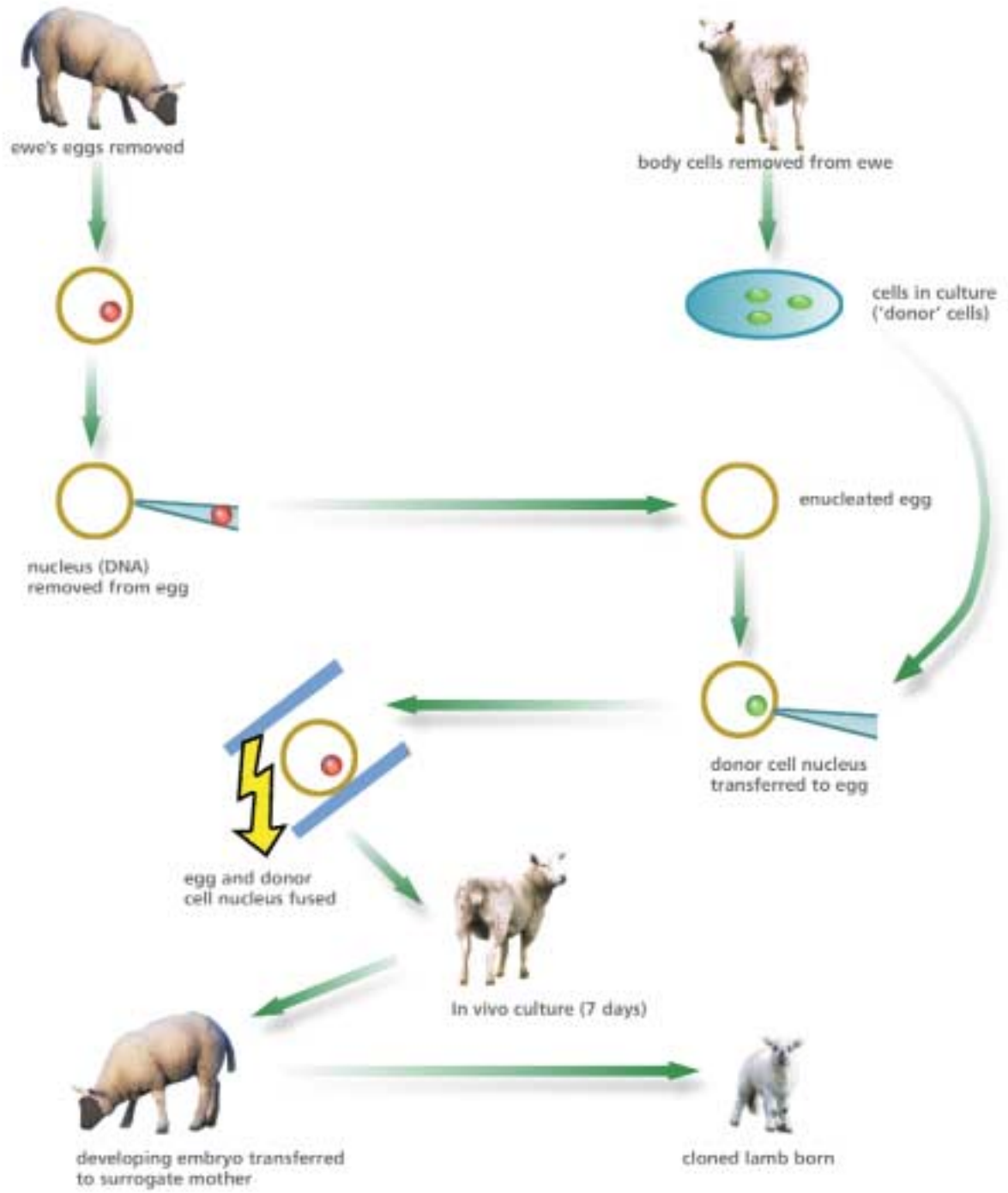


Diagram 2:

Diagram of the main steps in producing a cloned lamb by nuclear transfer from an adult ewe. The 'in vivo' step is sometimes replced by 'in vitro' laboratory culture. Similar methods are used for cloning cattle and pigs. (After FAWC 1998 Ref 7)

Part 2: Altered animals

5.0 Examples of transgenic farm animals

This section outlines some of the more recent experiments that have been reported either in the scientific press or the news media. However, it is almost certain that many more experiments are being carried out, particularly by biotechnology companies, than are ever reported to the public.

Genetic engineering experiments are often seen primarily as examples of scientific ingenuity. But this is a limited view. Such experiments as described below have caused both animal suffering and large-scale wastage of animal lives. Beyond that, the aims must also be questioned. Far too often, the objective of these experiments has been to intensify our use of farm animals. CIWF Trust would like to see a transfer of research effort away from genetic engineering towards research into farming methods that promote positive animal health and welfare.

5.1 Sheep

A large number of transgenic sheep have been born and some companies and research institutes keep flocks of them. Much of this has been carried out in Scotland, New Zealand and Australia.

5.1.1 Growth hormone (GH) genes

The Commonwealth Scientific Industrial Research Organisation (CSIRO) in Australia has been trying to control the amount of growth hormone in sheep in order to manipulate body growth, carcase composition and feed efficiency[12]. They inserted a sheep growth hormone together with a promoter that would let them control the gene expression. The first time this was tried, they found that "the transgenic animals were characterised by a very high basal expression of the gene, resulting in severe acromegaly [enlarged head or extremities] in the founder animals, all of which died before one year of age". In a following experiment, the transgenic sheep stayed in good health for 4 years, but they had less fat and greatly increased organ size; in a typical case, liver and kidneys were twice the normal size, ovaries and pancreas three times normal size, heart 28% larger and uterus 37% larger than normal at 3 years old. The transgenic sheep grew significantly faster than normal lambs up to 11 months[12].

5.1.2 Double-muscled sheep

In New Zealand, government scientists at AgResearch are attempting to produce lambs with bigger muscles, by genetic engineering of the myostatin gene, which controls muscle growth. According to their submission to the New Zealand Royal Commission on Genetic Modification in 2001, the development of transgenic sheep with the myostatin gene inactivated ('myostatin knockout sheep') could improve lamb value through quality meat production. It is known that double-muscling could well cause difficulties at lambing[49].

5.1 3 Extra wool growth – new biosynthetic pathways

According to a 1999 report, the CSIRO has also put genes from bacteria such as *E. coli* and *Salmonella* into sheep, with the aim of enabling them to synthesise cysteine, a sulphur-containing amino acid that is

essential to wool and muscle growth. A number of experiments have produced only a handful of sheep that express the gene, and only at a low level. The scientists concluded that trying to introduce new biosynthetic pathways may interfere with the sheep's existing biochemistry, and warn that the animals they want to modify probably already have "optimised gene combinations that are difficult to perturb without causing unexpected deleterious effects on animal phenotype". They say that "it may be necessary to trade some growth or fitness qualities for a gain in a particular production characteristic"[64]. By the spring of 2000 CSIRO reportedly had a flock of 120 transgenic 'ball-of-wool' sheep which grow faster, need less food and produce more wool than normal[65].

5.1.4 Human proteins in sheep milk

The biotech company PPL Therapeutics announced Tracy, its first transgenic sheep that expressed the human alpha-1 antitrypsin (AAT) gene in her milk, in 1991. PPL has since produced two transgenic AAT-carrying herds, in the UK and New Zealand. In May 2001 PPL had approximately 1100 transgenic sheep in Scotland, and about 800 transgenic sheep in New Zealand[66]. PPL received permission from New Zealand's environment regulator in 1999 to increase its flock to 10,000[67].

5.2 Goats

5.2.1 'Bio-steel' from goats

The Canadian biotech company Nexia has bred transgenic goats to produce "BioSteel" in their milk. This is the spider silk protein, stronger and more flexible than steel, which could be used for bullet-proof vests and the aerospace industry[68]. Nexia uses a trademark breed of early-maturing goats, named BELE ® (Breed Early Lactate Early). Embryos are extracted from BELE ® females, transfected with foreign genes and re-implanted in ordinary females as surrogate mothers[69]. By mid-2000 2000 the company reportedly had 150 transgenic goats[70].

5.2.2 Pharmaceutical products from goats

Transgenic goats with human genes have been produced by the biotech companies Nexia and Genzyme Transgenics, to produce human proteins, including antibodies and human antithrombin III, in their milk. Genzyme Transgenics has produced a total of 14 proteins in usable quantities (over 1 gm per litre of milk), from transgenic goats. Goats can be hormonally induced to lactate at 2 months old (several months before sexual maturity)[71,72]. CIWF Trust is totally opposed to inducing pre-pubertal lactation via hormone treatment. The procedure is certain to be distressing to such young animals.

5.3 Dairy cows

5.3.1 GM milk for food processing

Dairy cows are being engineered to give particular properties to their milk, either for drinking or for processing into other dairy products. US scientists are trying to modify the genes for various casein and whey proteins (the major proteins in milk) to alter the balance of fat and protein in cows' milk. Fat and protein content affect the usefulness of milk for processing into cheese or other dairy products. New Zealand government scientists aim to produce herds of transgenic cows, whose milk will be modified to reduce beta-lactoglobulin, an allergen for some people[49]. Other uses of trangenic cows envisaged at a US dairy institute were: to increase curd firmness, increase calcium content, change texture (of cheese), increase digestibility, increase *Salmonella* and *Listeria* resistance, reduce costs and even mimic human breast milk[73,74].

Dairy cows bred to produce very high yields of milk often suffer from mastitis (see Section 2.1.3). Mastitis is a very painful inflammation of the udder, usually caused by bacterial infection. Dairy scientists are now suggesting that cows could be engineered to resist mastitis, for example by making them produce more of the antibacterial protein lysozyme in their milk[75,76]. CIWF Trust believes that the attempt to genetically engineer mastitis resistance is a misguided approach to a problem that could be dealt with by better dairy cow husbandry and breeding for improved health.

5.3.2 Human breast milk from cows

A number of companies have experimented with producing human milk proteins in cows' milk, such as human casein and α-lactalbumin. In 1997 the biotech company PPL announced that they had genetically engineered a Holstein calf, Rosie, to produce human α-lactalbumin to be used as a nutritional supplement. One aim is to use these proteins to manufacture baby milk (infant formula) based on human milk as a nutritionally superior alternative to baby milk based on either cows' milk or soya milk, both of which can cause allergic or other adverse effects on babies[27,77]. Scientists in China are also said to be trying to breed cows to produce milk similar to that of human nursing mothers[78].

In one published set of experiments, to create transgenic cows producing human a-lactalbumin, scientists injected the human gene into 11,500 zygotes taken from cows. Developing embryos were transferred into 478 surrogate mother cows, of which 90 calved, all by Caesarean section. The calves were tested by taking blood from the jugular vein at 2 days old and by ear-notching. 9 calves (fewer than 0.1% of the injected zygotes) were found to be transgenic. One of these was hormonally induced to lactate at 6 months old to check for the protein in her milk. Three of the non-transgenic calves were born deformed or dead and 30 of them were killed to provide samples of lung, liver, bone and other tissues[79].

Rosie (pictured in 1997), a Holstein dairy calf genetically engineered by the biotech company PPL Therapeutics to produce the human milk protein alpha-lactalbumin in her milk. Rosie was hormonally induced to lactate when she was around 8 months old, in order to check whether her milk contained the human protein
© PPL

5.3.3 Pharmaceutical proteins in cow's milk

Because of their size and large udder capacity, cows are a prime target for producing pharmaceuticals in bulk, notably in the US and in New Zealand.

By 2001 New Zealand's AgResearch was reported to have a small herd of cows pregnant with transgenic calves carrying a human myelin protein gene, with the objective of producing large amounts of the protein in their milk, for possible use in treating multiple sclerosis[49]. PPL in 2000 was planning "immuno cows", whose own immunoglobulin genes have been inactivated and replaced with human immunoglobulin genes that would produce human antibodies[22]. Another US company is producing human polyclonal antibodies in the blood of a herd of transgenic cattle using a similar strategy[23]. The biotech companies Infigen and Pharming have collaborated to produce cloned transgenic cows for protein production (see Section 6.1.2).

5.4 Pigs

5.4.1 Growth hormones

"In the majority of reported studies with GH transgenic pigs, GH was constitutively expressed… in sufficient amounts to have a number of deleterious side effects including lameness and infertility"
Nottle *et al.* , *Transgenic Animals in Agriculture*, 1999[11]

There is a long history of trying to increase growth of muscle (lean meat) on pigs, as the public demands lean meat and the farmers demand increased feed conversion efficiency and lower costs from their animals.

The earliest and best known example is the 'Beltsville pigs', born at the USDA Beltsville laboratories in the mid 1980s, genetically engineered to carry human and bovine growth hormone genes. The animals suffered a range of severe health problems, and some were unable to stand[80]. In spite of this, efforts to put growth hormone genes into pigs continue in a number of laboratories. More recent experiments show that the problems caused by uncontrolled production of growth hormone in the pigs' bodies have not gone away. Scientists admit that in the control of expression of growth hormone has been "unsatisfactory"[11] (see Section 9.1.2).

Australian meat industry scientists have experimented with the porcine growth hormone gene and the human metallothionein promoter, which should enable the gene to be controlled by zinc in the diet. In their experiment, 289 piglets were born live, of which 88 were transgenic (2.8% of the injected embryos) and the gene and switch seemed to be working in several of them. But 8 of the 88 piglets had high levels of growth hormone expressed in all parts of their bodies and were euthanased. A number of the surviving piglets grew faster and needed less feed than normal piglets[11].

Scientists at Beltsville have experimented by putting the human insulin-like growth factor 1 (IGF-1) and an avian regulatory gene into pig embryos. 167 piglets were born to 51 mothers, of which only 17 piglets were transgenic. The concentration of IGF-1 in the transgenic pigs' muscles ranged between twice and 170 times as high as normal. Two of the transgenic female piglets died suddenly at 6 months old and one of these was found to have inflammation of the heart valves and cardiac haemorrhage. It is likely that these deaths were the result of expression of IGF-1 in heart muscle[81].

One of the 'Beltsville' pigs: given growth hormone genes.

5.4.2 The double-muscling gene

A mutation of the myostatin gene causes 'double-muscling' in some beef cattle breeds. This is known to cause welfare problems, including difficulty in calving. Now that the gene controlling 'double-muscling' is known, there are attempts to engineer the same mutation into a number of other farm animal species. A USDA research institute is investigating modifications of the myostatin (growth differentiation factor-8) gene with the aim of stimulating muscle growth in pigs[82]. There is no evidence as yet on whether or not this mutation will also lead to birthing problems for double-muscled pigs.

5.4.3 Injections of growth hormone gene

Scientists in Houston have experimented with a version of the growth hormone gene that they can

inject straight into pigs' leg muscles[83]. The scientists claimed the average body weight of the DNA-injected pigs was 37% higher than controls at 2 months old[84]. Chinese scientists are trying to inject growth hormone gene into pigs' muscles by using the adeno-associated virus to carry the gene into the muscle cells[27].

5.4.4 Genetically engineered docility

Pigs are very intelligent animals with a natural curiosity and need to explore their surroundings. When bored and overcrowded in factory farms, they tend to fight and cause damage to each other. Scientists at Purdue University are reported to be working to identify genes associated with aggression or stress in pigs kept for meat, with the aim of being able to "knock out" such genes. The aim is to achieve an increase of 20-25% in growth rate of the transgenic pigs. The leading scientist explained that if aggressive pigs 'hog the trough' and eat more than they need, "that's just nutrients going down the drain", while less aggressive pigs "fail to grow to their potential"[85].

5.4.5 Transgenic pigs for xenotranplants

See Sections 6.3.2 and 8.0.

5.5 Chickens

5.5.1 Faster growth and resistance to disease

In spite of the well-documented health and welfare problems caused by over-rapid growth of broiler chickens, scientists in the US and elsewhere during the 1990s genetically engineered either bovine or avian growth hormone genes into poultry, with the aim of speeding growth[27]. As well as growth rate, breeding companies are using genome analysis to produce chickens resistant to common farm diseases such as coccidiosis, *Salmonella* and *Campylobacter*, and also to require less feed, thus reducing their veterinary and feed costs[86]. A leading company, AviGenics, says that they can benefit the broiler industry by increasing disease resistance against *Salmonella* infection and coccidiosis and by 'targeting' expression of genes enhancing "muscle fiber hyperplasia and hypertrophy" (excessive muscle growth)[86,87].

Using the latest bird stem cell technology, the University of Wisconsin-Madison aims to breed flocks resistant to commercially damaging diseases, such as avian influenza and Newcastle Disease (fowl pest)[62,88]. It is likely that the chicken breeding companies, who are still aiming for faster growth rates, will move on to genetic engineering when the technology is established.

5.5.2 Heat stress

Intensively farmed poultry in hot weather suffer badly from heat stress in crowded sheds and many die from it. Scientists are trying to engineer poultry that can withstand these conditions. Scientists at Alexandria University put DNA from heat-resistant bacteria *Streptococcus agalactia* into chicken eggs and then reared the chicks in a temperature of 35 °C (95° F). Some of the birds showed tissue damage in the testes, liver, gizzard, heart and spleen[89]. In Israel[90], scientists used genome analysis and selective breeding to create chickens with the 'naked-neck' gene and the 'frizzle' gene, which has been found to increase their resistance to heat stress when they are kept at 32° C .

5.5.3 Pharmaceuticals in eggs

A US company, Geneworks, has a flock of 60 transgenic hens producing human growth hormones and antibodies in their eggs. Another company, Avigenics, has hens that produce human interferon and have passed on the gene to their progeny. The company already has transgenic cocks for breeding.

During 2001, at least 4 US companies and the Roslin Institute announced programmes to produce biopharmaceuticals, such as antibodies, blood products and enzymes in transgenic chicken eggs, including use of nuclear transfer[53,57,87,91-93]. Transgenic chickens are seen as a useful method of antibody production, partly because the regulatory obstacles are likely to be fewer (chickens are already used in vaccine production), and also because of the speed of reproduction of chickens and the low cost of egg production[28].

Although most GM experiments do not involve invasive procedures on hens, there is a lack of information on the health of GM chicks produced and the frequency of abnormalities and deformities. Hens kept for biotechnology experiments are frequently confined in cages, a system that is being phased out on farms in the European Union on welfare grounds.

5.6 Farmed fish

Intensive fish farming is a rapidly growing global industry which has already raised very serious welfare and environmental concerns[94,95]. The breeding of fish in intensive fish farms is already far from natural. Reproduction of farmed fish such as salmon and trout is done by 'stripping' eggs from brood females and milking breeding males for 'milt'. Females and males are generally anaesthetised and are sometimes killed as part of this process.

5.6.1 Sex reversal and chromosome manipulation

Raising only sterile female fish is seen as advantageous for growth-rate and flesh quality. 'All female stocks' are achieved by breeding from pseudo-males produced from genetic females by testosterone treatment. Their all-female offspring can then be made sterile by shocking the just-fertilised eggs so that they become triploid (they have 3 sets of chromosomes instead of the normal two[96,13]). Triploid (sterile) males can also be produced. The two methods ('all-female stocks' and induction of triploidy) are prohibited under organic fish farming rules in the UK.

5.6.2 Genetic engineering experiments.

The most usual aims of fish genetic engineering experiments are to insert extra growth hormone genes in order to increase growth rate. Experiments have been carried out on many species, including trout, salmon, catfish, tilapia, coho salmon, chinook and carp. A 1999 review by scientists from the US and Canada lists the number of genes or 'promoters' that have been experimentally put into fish. These include DNA from viruses and non-fish vertebrates, including humans and mice, as well as a variety of fish genes. The greatest effects have been found by using fish growth hormone genes; "When introduced into salmonids, such gene constructs elevate circulating GH levels by 40-fold in some cases …and result in approximately a five to 11-fold increase in weight after 1 year of growth"[13]. A British Government patent application states that the largest transgenic fish were 37 times heavier than normal at 12 months old and transformed to being 'smolts' (ready for migration to sea) 6 months earlier than normal[27]. The UK government is reported to be funding genetic engineering experiments worldwide, aimed at producing fast-growing transgenic fish for human consumption[97]. These experiments have serious environmental and regulatory implications because of the likely escapes of farmed GM fish (Section 5.6.4-5.6.5).

Experiments are also taking place on how the myostatin gene (which limits muscle growth in mammals) operates in fish such as catfish, trout, bass and tilapia, with a view to increasing muscle growth. Since some experiments suggest that myostatin may influence a number of different body cells and organs in fish, not just muscle cells, the possible welfare consequences of these experiments are very serious[98,99].

5.6.3 Welfare of GM fish

"In GH transgenic salmon, the endocrine stimulation can be elevated to pathological levels in some cases, and excessive and deleterious deposition of cartilage analogous to the mammalian acromegaly syndrome [abnormally large bones, such as the skull] has been observed. The effects can be sufficiently severe such that impaired feeding and respiration may result in reduced growth and poor viability" . Dunham and Devlin, *Transgenic Animals in Agriculture* 1999[13]

Unnaturally high levels of GH are damaging to the health of fish, as to other animals. Fish that had "extraordinary growth rates" as a result of genetic engineering were found to have enlarged skulls[13]. Apparently these deformed transgenic fish were unable to feed or breathe properly. A subsequent experiment reported in *Nature* in 2001 found that the GM domesticated trout developed skull abnormalities and all of them died before reaching sexual maturity[100,101].

How would escaped transgenic fish survive in the wild? There is evidence that some transgenic fish could survive better than natural fish. Other studies have shown transgenic fish are worse at swimming and at avoiding predators and are not able to grow faster than normal fish in wild conditions where they have to find their own food[13]. From the welfare point of view, it seems likely that fish engineered for large appetite and fast growth could suffer considerably in the wild.

5.6.4 Damage to wild fish – the 'Trojan gene'

A major worry about commercial farming of transgenic fish is that if the fish escaped (as large numbers of farmed fish do) they could damage wild populations, either by breeding with them or by competing with them for food. Researchers at Purdue University reported in 2000 that transgenic fish do not survive well and that they would pass on their negative traits to wild fish. The result could be that they wipe out wild fish stocks. Computer models showed that 60 transgenic fish could lead to the extinction of a population of 60,000 fish in 40 generations. The researchers predict that "a transgene introduced into a natural population by a small number of transgenic fish will spread as a result of enhanced mating advantage [the fish are larger], but the reduced viability of offspring will cause eventual local extinction of both populations"[102,103].

The industry states that GM fish in commercial production would be sterilised, so they would pose no risk if they escaped from fish farms. But sterilisation is not always effective. Research published in 1999 in *Marine Biotechnology* showed that in transgenic males "There were also some spermatozoa present in the testes of some triploids, which could be indicative of reproductive functionality"[104].

5.6.5 Risks of commercial GM fish farming

North American fish breeding companies are reported to be anxious to get approval for commercial sales of GM fish. These fish would reduce both the

time taken to reach slaughter weight and feed costs, by growing up to 5-10 times faster than normal in their first year. One company has engineered Atlantic salmon to produce growth hormone in the liver as well as the pituitary gland (the normal case)[103]. The Canadian company Seabright was granted a European patent in July 2001 for a growth hormone gene to increase the growth rate of Atlantic salmon by 8 times[105]; Aqua Bounty farms is reportedly seeking commercial approval for salmon that grow 10 times as fast as normal[106].

Scientific opinion agrees that GM fish should not be allowed in areas where they could escape, such as coastal waters. The Royal Society of Canada and the UK's Royal Society believe that the escape of GM fish could pose an environmental risk to natural populations and recommend "a moratorium on rearing GM fish in aquatic net-pens, with approval for commercial production being conditional on rearing of the fish in land-locked facilities"[4,107].

From the point of view of protecting the welfare of farmed fish, the conservation of wild fish and the environment, CIWF Trust believes there is no case to be made for genetic engineering in fish farming.

6.0 Examples of cloned farm animals

"[Nuclear transfer] is expected to herald a new era in biotechnology, with opportunities to generate animals for various biomedical applications (including the production of pharmaceutical proteins, food with improved nutritional and health properties, and organs for transplantation) and livestock with enhanced agricultural production characteristics"
Wells, *Agricultural Science* 1999[5]

We have seen that the main uses envisaged for farm animal cloning are for multiplication of highly productive animals for commercial farming and as an enabling technology for genetic engineering. Cloning has now been applied to cattle, sheep, goats, pigs and chickens. A New Zealand research institute believes that, "The most immediate impact of nuclear transfer will be in combination with gene targeting technology to introduce precise genetic modifications to the cultured cells in the laboratory, resulting in the production of cloned, transgenic livestock"[5].

Serious questions need to be asked about both the practice and the aim of farm animal cloning. Cloning has led to large numbers of invasive experimental procedures on animals and large-scale wastage of animal life (Section 9.2). The aims – to produce genetically identical farm animals - are highly questionable from both health and environmental viewpoints. CIWF Trust does not believe that cloning will ever be an acceptable method of producing farm animals, for any commercial purpose.

6.1 Cattle cloning

Cattle are potentially very valuable animals and this fact has led to considerable investment in cattle cloning, taking place in universities, research institutes and biotechnology companies. "Hundreds of calves" were cloned in the US during the 1980s, according to a survey in *Science* in 2000, few of which survived[110]. Cattle cloning has mainly taken place in the US and New Zealand (for example at Colorado State University and the companies Advanced Cell Technology, Infigen, Cyagra and Geron in the US and at AgResearch in New Zealand). At AgResearch 10 live calves have been cloned from one cow[5] and at the

University of Georgia 8 live calves have been cloned from one cow (the result of transferring embryos to 100 surrogate mother cows)[8]. In 2001 the company Infigen claimed to have cloned 120 healthy cattle[109].

But cattle cloning has also been attempted in laboratories around the world, including Australia, Japan, Italy, Holland and France. By 2000, total numbers of cloned cattle were estimated at around 300[110].

Holly and Bell, cloned by the Netherlands biotech company Pharming in 1998. In 2002 Holly and Bell were still living in the Netherlands but because of financial difficulties their future may be uncertain.

6.1.1 Large scale cloning for farming

Some scientists and companies have suggested that cloned cattle embryos could be sold instead of semen to increase the productivity of farmers' herds, by making multiple copies of the most productive animals. This process of cloning for commercial reproduction has already begun. Dead or injured top-producing cows and bulls from the dairy and beef industries have been 'immortalised' by cloning calves from their cells[111]. By mid-2001 a US company claimed to have 18 dairy clones producing 'normal' milk after calving[112]. Another US company has sold clones of a top-producing dairy cow to a commercial farmer. The US Holstein Association has decided that clones will take the name of their DNA donor animal, with the suffix 'ETN'[113].

Cloning is seen by some as a potential animal mass production method to multiply 'elite' farm animals around the world. The company Genetics Australia envisaged in 1998 that cloned embryos, from clone "families" of 100,000, could be sold to farmers at about $30 each. In this view, cloned embryos with a 50% pregnancy rate (the same rate as in normal embryo transfer) would be attractive to dairy farmers. These "families" could be kept frozen for 4 years. The scientists add that, "Family sizes of 1 million would be too large if they were all located in Australia; there would be a danger of a lack of diversity". Embryos delivered in a 'straw', instead of semen, could be implanted by existing AI technicians. Alternatively, to avoid the ET technology, there could be contract delivery of cloned dairy calves, at a price competitive with semen . Some believe that cloned bulls for mating could "virtually bypass AI" in the beef industry[114,115].

The US company Cyagra, which has sold 2 cloned embryos of a prize dairy cow to a dairy farmer, believes that cloning is economic even at today's rate of up to $25,000 per embryo. A spokesperson commented, "Push the price down to $10,000 and there would be 100,000 animals that it would be economical to clone, and in the $5000 range, millions" [116]. In this scenario, Holstein dairy cattle clones could be sold worldwide, including to China, to replace lower-yielding local cattle[117,118].

Cloning on this scale is estimated to use 4 surrogate mothers for every clone born. Australian scientists calculate that the production of 100,000 identical animals for one clonal line would require 2 million successful fusions of donor cell and oocyte and 400,000 embryos transferred to surrogate mothers[115].

6.1.2 Transgenic cloned cows for 'pharming'

Cloned transgenic cows could be used to produce large quantities of human proteins, or other foreign proteins, for pharmaceutical or industrial use. In the US, the Netherlands company Pharming, in collaboration with Infigen, has set up a farm in Wisconsin to produce cloned transgenic cows with human proteins in their milk. These were said to number 45 in 2001, mostly for producing fibrinogen and collagen[119], when this collaboration ended after Pharming went into receivership[120].

6.2 Sheep and goat cloning

Individual sheep, producing meat and wool, are not very valuable animals. So far, most of the cloning effort put into sheep has been with the aim of using the cloning technology to aid genetic engineering, rather than to multiply normal sheep. The genetically engineered cloned sheep would be intended to produce high value protein products for pharmaceutical or other uses. Sheep cloning has mainly been carried out in the UK and also in New Zealand, for example at the research institute AgResearch. Polly, produced in Scotland by the Roslin Institute and PPL Therapeutics, was the first cloned transgenic sheep, carrying the human gene for Factor IX, a blood-clotting protein[48]. In 2000, cloned lambs were genetically engineered with the AAT gene by what was described as a more precise method ('gene-targeting') of putting the foreign DNA into cultured foetal cells. In this experiment only three surviving lambs were produced, out of 80 embryos implanted in 42 ewes[10].

Cloning technology also allows scientists to try to delete genes from an animal's DNA. The Roslin Institute has deleted two genes from cloned sheep, one of them the prion protein gene associated with scrapie and BSE. In these experiments, 120 embryos were transferred to 78 ewes and 8 lambs were born, 4 live and 4 dead. The 4 live lambs all died within two weeks[15].

Cloned transgenic goats have also been produced, particularly by the Canadian and US companies Nexia and Genzyme Transgenics[121] (see Section 5.2 and 7.0).

6.3 Pig cloning

The uses that are foreseen for pig cloning are either to reproduce high-yielding animals for meat or to produce genetically engineered pigs with 'humanised' organs for xenotransplants. Pigs could also be used for pharming proteins. The birth of the first cloned piglets was announced in mid-2000[9,122].

6.3.1 Pig cloning for meat

Companies in the US and in Japan are experimenting with cloning to produce pigs for meat. The Japanese National Institute of Animal Husbandry, in

collaboration with Prima Meatpackers, announced in 2000 that they had produced one black Meishan piglet cloned from a foetal cell. To produce this piglet, the scientists transferred 269 cloned embryos to 10 surrogate sows. Thirty four piglets were born, of which only one was a clone[122]. The University of Athens, in Georgia, and associated companies are aiming to use cloning on a mass scale to multiply valuable animals in collaboration with Smithfield Foods, one of the world's largest pork producers. The aim is to save time on selective breeding and help pork producers create leaner bacon and meatier chops[123].

6.3.2 Pig cloning for xenotransplants.

Cloned piglets announced by the biotech company PPL in 2000 were seen as a first step to breeding transgenic pigs for xenotransplants. PPL (working in Scotland and the US) used adult cells to clone from and produced 5 live and "extremely healthy" piglets by a new 'double nuclear transfer' method. According to the scientists, a total of nearly 600 embryos were transferred to 10 sows, as many as 100 embryos being put in a single sow. Two of the sows become pregnant and the five live piglets were born from one sow by Caesarean section. The total number of pig oocytes used was 2100, according to the report[9]. PPL later produced a litter of 5 cloned piglets which had a foreign 'marker gene' put into their DNA, a first step to genetically engineered pigs[125] (see Box Section 8.0).

Numbers of cloned piglets worldwide are now growing. In 2000 the US companies Infigen and Imutran announced they had produced 4 cloned piglets from foetal cells cultured *in vitro*[126]. The experiment involved putting over 100 embryos into each surrogate mother sow, "consistent with the low viability of NT embryos". By 2001, Infigen claimed to have cloned 50 piglets in total, some of them transgenic[127]. In early 2002 PPL and Immerge BioTherapeutics both announced litters of cloned 'knock-out' piglets, lacking one copy of the α-1,3 galactosyl transferase gene, associated with the rejection of pig organs by the human immune system [19,128]. At least two biotech companies are cloning transgenic miniature pigs for xenotransplantation (miniature pigs have suitable sized organs for human use). One of the intentions is to produce breed a line of minature pigs that "do not appear" to have Porcine Endogenous Retrovirus that could infect human cells[129] (see Section 11.1-2).

6.4 Chicken cloning.

Cloning of poultry is being promoted for a number of uses: to produce pharmaceuticals or other proteins in eggs; for rapid breeding to meet a particular market demand for meat chickens; or to breed strains with desirable characteristic such as disease resistance. It seems likely that companies will aim to use transgenic chickens for pharmaceutical production and cloned (but non-GM) chickens for the food market. The Roslin Institute, AviGenics, Origen Therapeutics of California and Embrex all announced chicken cloning programmes in 2000[86,130]. Using the stem cell method, which differs from nuclear transfer, around 95% of the chick's cells would be derived from the 'donor' chicken.

According to a *New Scientist* report of this research, the technique would enable breeding companies to supply farmers with millions of eggs of a particular strain of chicken in a matter of months or even weeks, matching all the varieties that the market might demand[130].

6.5 Human-animal hybrids

Scientists interested in producing human embryonic stem cells for medical research have transferred the DNA from human cells into animal egg-cells and allowed them to develop into early embryos. This is seen as useful for stem cell research because of the difficulty of obtaining human eggs in large numbers.

Nuclear transfer of human DNA to animal eggs has been reported for cattle, pigs and rabbits. In 1998 a senior researcher at the US company Advanced Cell Technology announced that he had transferred some of his own cells into cows' eggs and grown the embryos for several days[44]. Two companies, Stem Cell Sciences (Australia) and BioTransplant (US) have applied for patents on the creation of human-pig cells for cloning. They are reported to have put the DNA of a human cell (taken from a foetus) into the egg-cell of a pig and have grown the embryo for a week. Although the embryo's DNA would be nearly all human, there would be about 3% contribution from the pig (mitochondrial DNA in the pig's egg cell)[131,132]. In 2001 Chinese scientists at the Sun Yat-Sen University of Medical Sciences replaced the nucleus of rabbit egg cells with skin cells taken from a 7-year old boy and let the embryo develop for around 3 days (to the 'morula' stage)[133]. It must be very likely that somewhere in the world some scientist will try to bring such an embryo to a further stage of development, if not to term.

7.0 Pharming: animal drug factories

Biotech companies are aiming to develop production herds of animals for 'pharming'. In pharming, transgenic animals are used to produce human proteins for pharmaceutical uses in various body fluids – milk, blood, urine and semen, from where they can be extracted and purified. Milk is the most popular fluid, because of ease of extraction and the large volumes that could be obtained from cows or large sheep flocks. In this case, the gene for the foreign protein is linked with a promoter gene that directs expression of the gene to the animal's mammary gland. Companies claim that some transgenic animals can produce 40 grams of the product per litre of milk[134]. Given that a very high-yielding dairy cow can give 10,000 litres of milk a year, the potential for large scale production is seen as commercially attractive. Sheep and goats, and even pigs and rabbits, are also being used. These smaller animals breed faster and start lactation sooner than cows, although they produce less milk. A review in *Trends in Biotechnology* for 1999 estimated an annual yield of 40kg of protein from a cow, 4kg from a goat, 2.5 kg from a ewe and 1.5 kg from a pig[8].

Pig semen is also being investigated as a protein source, by genetic engineering of the seminal gland[135], since male pigs produce large amounts of seminal fluid (200-300 ml per ejaculate, containing 30mg of normal protein per ml) and boars "can ejaculate 2-3 times a week, year round" [136]. Semen could be extracted from the transgenic boars daily[135]. The scientists commented "As semen is a body fluid that can be collected easily on a continuous basis, the production of transgenic animals expressing pharmaceuticals into their seminal fluid could prove to be a viable alternative to use of the mammary gland as a bioreactor"[136].

The production herds and flocks of transgenic animals can be built up in several ways. Transgenic animals that are capable of transmitting the transgene to offspring can be bred by conventional means. Alternatively, transgenic animals can be created by genetic engineering, possibly using nuclear transfer. In principle, large numbers of transgenic animals could be generated quite rapidly by cloning.

7.1 Overview of products and companies

By the later 1990s several companies were using transgenic animals to produce human proteins intended for use as biopharmaceuticals. These are molecules that often need to be made by living cells rather than by chemical synthesis. According to a 1999 industry survey, Genzyme Transgenics Corporation, PPL Therapeutics, and Pharming, in collaboration with Infigen, had a number of products in clinical development, including antithrombin III, α–1 antitrypsin, fibrinogen, bile salt stimulated lipase (BSSL), superoxide dismutase, Factor VIII and Factor IX, calcitonin, alpha-glucosidase, C-1 esterase inhibitor, collagen and lactoferrin, human antibodies and myelin protein. Companies have experimented with large numbers of proteins; Genzyme claims to have produced 65 different proteins in usable quantities from transgenic animals[72]. Only AAT, alpha-glucosidase and antithrombin III were noted as being in clinical trials, the rest being in preclinical development. The conditions targeted were cystic fibrosis, emphysema, Pompe's disease, coronary artery bypass grafting, pancreatitis, heart attack, arthritis, respiratory distress, bleeding, surgical wounds, gastrointestinal infections, thrombosis, osteoporosis, as well viral diseases and multiple sclerosis. PPL has produced AAT in sheep and antibodies in cows and has also used mice and rabbits; Pharming has used cows and also rabbits; Genzyme Transgenics and Nexia specialise in goats[26].

There is some evidence that biotech companies have found animal genetic engineering more difficult and costly than they anticipated. PPL, for example, have discontinued work on their blood-clotting factors, Factor VIII and Factor IX, possibly because their transgenic animals did not produce enough of the proteins. Of their lead products, AAT (possibly useful for treatment of cystic fibrosis and emphysema) , BSSL (a nutritional enzyme that breaks down fat) and fibrinogen (a surgical sealant), none has reached Phase III clinical trials, although AAT is expected to start these in early 2002[134]. PPL's sheep flocks in mid-2001 were still relatively small – 3000 sheep in Scotland, of which about 1100 were transgenic and 3500 in New Zealand, of which around 800 were then transgenic[66]. More than one pharming company was reported to be in financial difficulties during 2001[119].

7.2 Why they use farm animals

The public has been given the impression that pharming promises to give us medically-useful proteins that could not be obtained in any other way. This is often not the case. Recombinant proteins can be produced in a number of different types of 'bioreactor', either in mammalian cell culture (such as hamster cells), in bacterial cell culture, in transgenic plants and in transgenic animals. At present mammalian cells and bacterial cells are used commercially. Transgenic plants are potentially a

large-scale, low-cost production method[137,138]. Transgenic potato and tobacco are capable of producing complex proteins at 10%-50% of the cost of bacterial cell culture, according to German scientists writing in *Nature Biotechnology* [139]. Why do pharmaceutical companies use live farm animals, with all the experimentation and wastage of animals this entails?

One argument made in favour of using live transgenic animals is that they can produce large and complex bioactive human proteins, including those that need post-translational modification, such as glycosylation, folding and assembly, that bacterial cells are not able to do properly. Mammalian cell cultures and transgenic plants can also produce the bioactive proteins satisfactorily but mammalian cell culture cannot be done easily on a large scale and is relatively costly[137,138,140]. The second main argument is that transgenic animals could be very considerably less costly than mammalian cell cultures[25,137]. Animals are seen as a potentially cheap and large-scale production system. Once healthy transgenic animals were in production, the companies believe, "The cost benefit of transgenic production is due to the relatively low capital investment required to establish animal housing and production operations compared with the expensive fermentation and cell culture facilities" [134].

CIWF Trust is dismayed that decisions to use animals in pharming, when alternatives are clearly available, are being made solely on commercial grounds without a detailed ethical assessment. CIWF Trust believes that pharming is an unnecessary and retrograde step in our treatment of farm animals (see Section 13.2).

8.0 Transgenic pigs for xenotransplants

The advocates of using animal organs in humans (xenotransplantation) argue that pigs are ideal sources of xenotranplants because they are available in large numbers and because their organs are similar in size and nature to those of humans. They predict that clinical trials could start by 2005 and that the market could be worth $5 billion for solid organs alone[124,125]. The pigs would be genetically engineered to reduce the rejection of their organs by the human immune system.

During the 1990s large numbers of pigs for xenotransplant experiments (often for organ transplant to primates, including baboons) were bred in the UK. Between 1997 and 1999 at least 184 transgenic pigs were exported from the UK for breeding and research, to North America, Europe and Japan, according to the Home Office[141]. Numbers of pigs and monkeys were killed in UK xenotransplantation experiments between 1996 and 2000[142].

There is evidence that the xenotransplant experiments caused great suffering to the monkeys, arguably without demonstrating that pig organs can sustain life in primates[143]. In 1998 experiments at Cambridge, 13 cynomolgus monkeys given pig kidneys died between 7 hours and 35 days later, in spite of being immunosuppressed with cyclosporine, steroids and cyclophosphamide. Seven of the kidneys were transgenic. Although hyperacute rejection was avoided, three of the transgenic kidneys failed and the remaining four monkeys with transgenic kidneys developed severe anaemia[144]. In a subsequent experiment, pig hearts were put into the abdomens of baboons. The 9 baboons with inserted transgenic hearts lived between 10 and 99 days, when the last one was killed because of fever. Hyperacute rejection was avoided, but 6 of the transgenic hearts stopped beating due to acute vascular rejection[145]. By autumn 2000, the longest time a pig heart had kept a monkey alive in these and similar experiments was 39 days[132].

By 2001 it appeared that UK research using transgenic pigs for this purpose might be waning, with research at the Roslin Institute and Imutran (in the UK) ending. Active research to produce transgenic pigs continues around the world, particularly by the companies PPL, Immerge, Novartis, BioTransplant, Infigen and Nextran, among others. One objective is to produce pigs which can be said to be free of Porcine Endogenous Retroviruses (PERV), which has emerged as one of the main obstacles to gaining regulatory approval for applying the technology to humans[129] (see Assessment, Section 11.0).

Rejection of xenotransplants. A pig organ transplanted into a monkey or a human is rejected within a few hours by the process of hyperacute rejection. In hyperacute rejection, the body's 'complement system' destroys the foreign organ. The complement system is a series of chemical reactions by which the immune system recognises and destroys foreign cells. However, even if hyperacute rejection is avoided, the foreign organ is still subject to rejection over a period of days to weeks (acute vascular xenograft rejection). Beyond this, there are other types of rejection, including chronic rejection, which also occur in human-to-human organ transplants[146,128].

The objective of several biotech companies is to engineer pigs to produce human proteins that could block the hyperacute rejection of foreign tissue by the primate recipient (monkey or human). One way is to engineer the pigs to express the human decay-accelerating factor (hDAF or CD55) or other proteins which regulate the activity of complement (proteins involved in the immune system's attack on foreign cells). The biotech company Imutran produced "a colony of pigs transgenic for the human regulator of complement activity, human decay-accelerating factor (hDAF)" [144]. This approach is also taken by Nextran[129]. Another approach is to engineer the pigs to remove a sugar molecule on the surface of normal pig cells which is recognised by human antibodies . The biotech companies PPL and Immerge BioTherapeutics engineer pigs to disable the gene for the enzyme a-1,3-galactosyl transferase, which promotes the production of the particular sugar molecule on pig cells, by using cloning methods[9,128,19]. It is not yet known if the enzyme deletion would be useful in reducing either acute vascular rejection or longer-term xenograft rejection[128].

Part 3: Assessment

9.0 Animal welfare

"[M]any transgenic individuals may be unviable, abnormal or infertile, or have deleterious side effects which rule out their use." Smith et al., *Animal Breeding Abstracts* 1987[147]

The outstanding fact revealed by genetic engineering and cloning experiments so far is the extent of scientific ignorance. Often under commercial pressure, scientists are experimenting on farm animals well before they have adequate understanding of what they are doing. The inevitable result is risk of harm both to the animals, to consumers and to the environment. At this point, it is the risk and well-documented harm to the animals themselves that is most obvious. The future risks, in the event that the technologies become widely used in industry and farming, are wholly and unpredictable.

Scientists still know very little about how genetic engineering and cloning affects farm animals' genes and bodily development. As far back as 1987, scientists recognised the risk to the animals that genetic engineering involved. A researcher from the former AFRC (now incorporated in the BBSRC) at Edinburgh stated presciently,

> "Both the incorporation of exogenous DNA into a stable genome and the increased production of specific enzymes or hormones in a balanced biochemical / physiological system might be expected to harm rather than improve development and performance" [147].

A well-known biotechnologist from the US Department of Agriculture has queried whether cloning is safe enough for routine animal breeding;

> "Does the process of nuclear transfer create genetic disease?…Do some of the steps in the process .. serve as mutagens? I for one don't know" [25].

Given this level of ignorance, biotechnology experiments have caused and are causing immense harm to large numbers of farm animals. CIWF Trust believes that experiments on live farm animals cannot be justified at the present primitive stage of scientific knowledge of gene function, gene expression and incorporation of DNA into the animals' genome.

The calf on the left was cloned at the French agricultural institute INRA (reported in 1999). She appeared healthy up to 6 weeks of age when she developed severe anaemia and died. Autopsy showed that her immune system had not developed properly, acommon problem with clones.
© INRA

The New Zealand Royal Commission on Genetic Modification in 2001 was told by a government scientist that the possible welfare "areas of concern" of their research programme on sheep and cows included:

- **Caesarean section delivery of offspring**
- **Birthing difficulties of double-muscled animals**
- **Induction of lactation in young animals**
- **Health and well-being of cloned-transgenic animals**
- **Aberrant behaviour of genetically modified animals as against conventional animals**

L'Huillier, *Witness Brief to New Zealand Royal Commission 2001*[49]

9.1 Animal welfare and genetic engineering

The methods of genetic engineering, often described as 'precise', are in fact almost entirely hit-and-miss. This conclusion is borne out by the difficulties scientists and biotech companies have experienced so far. Scientists admit that they have failed to produce many healthy transgenic animals. According to a prominent Colorado State University scientist,

"Hundreds of millions of dollars were invested in transgenic farm-animal research between 1983 and 1997, much of it by the private sector primarily for producing pharmaceutical products. … Thousands of person-years of effort, much of it from the private sector, have been expended without yielding any product." [148]

This scientist points out that, after the creation of the GM animals, "the resulting line of animals must survive and reproduce successfully with little or no further technological interference. …Moreover, to be acceptable in production agriculture, the transgenic animals would have to be certified as healthy and not require special care. In the short term, few transgenic lines will meet the requirements for agricultural application" [148].

9.1.1 Random integration and expression of foreign genes

"The mechanism of transgene integration after pronuclear injection is unknown".
Eyestone, *Transgenic Animals in Agriculture* 1999[79].

Little is understood about how the foreign genes integrate into the animal's DNA, or what effect this may have. It is believed that between one and several hundred copies of the gene are integrated into the animal's DNA at one random site. It is unlikely that this will be in the right place in the chromosomes and usually the injected genes cause damage to the animal's DNA. Very few of the injected embryos survive. In US experiments, only 0.08% of injected cow embryos produced transgenic calves[79]. Of those animals born carrying the gene, less than half of them may express it, according to scientists at the USDA [149]. The result is that large numbers of normal animals are used to produce relatively few transgenic offspring. US biotechnologists estimate that to produce 1 transgenic animal they need to inject foreign DNA into either 110 sheep's eggs, or 90 goat's eggs or 1600 cattle eggs[74].

Scientists are unable to control the expression of the inserted genes, to make sure that this happens in the right tissues and at the right time. According to scientists who put foreign genes into dairy cattle;

> "expression is often inappropriate, occurring in unintended tissues (ectopic expression) or at developmentally incorrect times"[74].

Genes may interact with each other in unexpected ways. Scientists attempting to change cows' milk genes found that a "major gene for milk and fat yield" was tightly linked to a lethal genetic disorder called degenerative myeloencephalopathy ('weaver')[76].

A UK cloning expert has described the problem vividly:

> "If the novel DNA…is incorporated into a part of the host DNA that contains coding sequences, then clearly it can be highly disruptive….It is one thing to put a gene into a new cell and it is quite another to ensure that the gene is then expressed properly. ..it could be damaging to the animal if a gene that was intended to express in the mammary gland also expressed itself in muscle or brain or what you will - especially if, for example, the product of that gene was a clotting factor. But then, in principle a protein like a clotting factor might be produced exclusively within the mammary gland but then leak into the rest of the body.." [63].

In the case of experiments on growth hormone genes, it is not going too far to say that these have often been a welfare disaster for the animals involved. The intention is to increase the production of growth hormone affecting the growth of muscle (meat). Clearly if excess growth hormone is expressed in bones or internal organs the consequences can be appalling - animals with grossly enlarged heads, abnormal bone growth or enlarged hearts or other organs. These animals either die or have to be euthanased early in life. Sometimes excessive growth hormone leads to heart failure as the animals are growing up.

Cloning is seen by some scientists as the solution to the randomness of pronuclear injection methods. But experiments on cloned, transgenic animals can have exceptionally high mortality rates (Section 9.2).

9.1.2 Effects of the transgene

Even when the transgene is functioning as intended, the effect of producing a foreign protein can adversely affect the transgenic animal. To produce human antibodies, scientists have disabled animals' immunoglobulin genes, part of their own immune system. The biotech companies PPL Therapeutics and Immerge BioTherapeutics disabled the gene for α-1,3-galactosyl transferase in pigs destined for xenotransplants, without knowing how it would affect live pigs. The gene deletion could be damaging, or even lethal for animals with both copies of the gene disabled[128]. One of the company scientists noted, "Even if the gene can be deleted …the structure may provide some essential biological function in pigs and thus destroying the a-1,3-GT enzyme could be deleterious to the animals"[25].

When female mammals are used for pharming, there must be questions over how much or what types of foreign protein can be produced without damaging the udder. Already spider-silk and collagen have been produced in transgenic animals' milk. Collagen is an insoluble fibrous protein which is part of the structure of skin, tendon and blood vessels.

Scientists are aware of the potential for damage. A patent application for collagen production in transgenic bovines and other animals, from Gene Pharming Europe (Netherlands) and Collagen Corp. (US), noted "Surprisingly, the transgenic animals of the invention exhibit substantially normal health. Secondary expression of procollagen in tissues other than the mammary gland does not occur to an extent sufficient to cause deleterious effects. Moreover,

virtually all exogenous [foreign] procollagen produced in the mammary gland is secreted so that no significant problem is presented by deposits clogging the secretory apparatus". Scientists who produced human milk proteins in transgenic cows warned in 2001 that "exceptionally high levels of recombinant polypeptide production may adversely affect the production of endogenous [cow's] milk protein and/or have adverse effects upon the mammary secretory gland". These scientists suggested limiting foreign protein production to 10-15% of normal bovine milk protein content [27]. It would be almost impossible to enforce such limits in commercial practice.

Will unfit animals be created by genetic engineering? Most of the genetically engineered animals created so far could not survive in normal farming conditions. Most animals with "extreme phenotypes" are not what nature intended and "dramatic changes in physiology usually are incompatible with normal lifestyles", according to a University of Colorado scientist[148]. But unhealthy and abnormal animals may still be profitable. "Although animals with such phenotype would not survive in nature, the farmer who uses them in production agriculture may survive well economically"[148].

9.2 Animal welfare and cloning

"Something in the recipe is fundamentally wrong"
Pennisi and Vogel, *Science* 2000[10]

Animal cloning scientists have made strong public statements about the risks to humans from reproductive cloning, arising from scientists' poor understanding of the processes involved. Large numbers of farm animals have already been subjected to these risks. According to a Roslin Institute cloning expert, only between 0.04% and 1.7% of cloned embryos develop into live offspring, depending on the type of cell used for cloning. Development is least likely if adult cells are used. Of the developing embryos transferred to recipient ewes, only between 3.4.% and 7.5% develop into live offspring. Some of

Mortality in recent cloning experiments. Table shows the number of embryos and surrogate mothers needed to produce small numbers of surviving young by cloning, taken from published research where the numbers are recorded. The appproximate number of offspring produced in normal farming conditions by the same number of mothers is given in the last column.

Species [ref.]	Embryos created	Embryos transferred	Surrogate mothers	Live births	Born dead	Surviving offspring	normal offspring
sheep [1]	507+	120	78	4	4	0	125
sheep [2]	417	80	42	14	5	3	67
cattle [3]	n.k.	20	14	2	n.k.	1	12
pigs [4]	n.k.	586	10	5	n.k.	5 (3 mths)	100
pigs [5]	n.k.	328+ [1]	28	7	n.k.	4 (3 mths)	280

[1] Denning et al., 2001[15] [2] McCreath et al. 2000[10] [3] Zakhartchenko et al. 1999[17] [4] Polejaeva et al. 2000 (reported when piglets 3 months old)[9] [5] Lai et al. 2002 ([1] 328 cloned embryos were transferred to 3 of the 28 sows)[19].

the cloned lambs are unusually large and there is

> "a substantially greater incidence of peri-natal loss… often associated with congenital abnormalities, in the cardiovascular or urinogenital systems… Gestation is typically extended by several days and the onset and progress of parturition is often slow. Despite the prolongation of gestation, lung development in the lambs is sometimes immature" [14].

Cloned offspring are frequently abnormal and the birth itself is often difficult. A UK expert reportedly told US National Academy of Sciences meeting in 2001 that for cow cloning, 37% of live offspring die; with sheep 27% of the offspring die; for goats 40% of the offspring die[150]. Other scientists quote even higher death-rates; according to French scientists, 40%-74% of cloned animals have died just before or after birth[151]. For cattle cloning, scientists say that "embryos reconstructed by nuclear transfer are slow to be born (pregnancy is prolonged) and, commonly, are thirty per cent large than normal, or even more. Birth then becomes difficult and painful" [63]. This is called "Large Offspring Syndrome" and scientists admit that it is "neither predictable nor reproducible" [152].

When the cloned animals are also transgenic, recent losses have been very high. Eleven out of 14 liveborn cloned transgenic lambs died shortly after birth in a cloning experiment reported by the biotech company PPL Therapeutics in 2000. Five more lambs were born dead. All births were by induction or Caesarean section[10]. All of 8 'knockout' lambs cloned from cultured cells died in an experiment reported by the Roslin Institute in 2001. Four were born dead, 3 died shortly after birth and the fourth was euthanased at 12 days old due to heart and lung failure. The dead lambs had abnormalities in their placentas and in their livers, hearts and kidneys. The scientists concluded that the long culture and genetic engineering of cells used for cloning may be "detrimental to development"[15].

In 2000 the prestigious journal *Science* surveyed published animal cloning experiments. Cloning scientists reported that only 2 or 3 live offspring result out of every 100 attempts to clone an animal. Pregnancies often miscarry and a significant fraction of animals born are abnormal. The liveborn calves often have "lungs like premature babies" or potassium levels in the blood so high that "the calf should be dead". One prominent scientist admitted, "What we still have is a black box". Another said, "Just because you've got offspring doesn't mean they're normal"[110].

Cloning may turn out to be a fatally flawed technology. One suggestion is that the DNA of clones has abnormal methylation of DNA (methylation has a role in regulation of gene expression). Korean scientists reported in *Nature Genetics* in 2001 that they had found definite differences in methylation between the DNA of cow embryos created by nuclear transfer and the DNA from embryos created by IVF[153]. There is evidence that gene expression may not be correctly regulated in clones. US cloning scientists have found

> "widespread dysregulation of genes in cloned animals" [20].

Results from published cloning experiments, to 2000. Source: Pennisi and Vogel 2000[110].

Species	nuclear transfers	embryos transferred	live births	live births per embryo transferred
cows	1912+	225 +	36	16%
goats	125	85	3	4%
sheep	1921	327	22	7%

9.2.1 Deaths of cloned offspring

The following examples of typical experiments reported between 1999 and 2001 indicate the health problems of young cloned animals:

A calf cloned at INRA, the French agricultural research institute, appeared normal at birth but at 6 weeks old suffered a sudden fall in its level of white blood cells and haemoglobin and died in a week from severe anaemia. The scientists found that its thymus, spleen and lymph nodes (vital to the immune system) had not developed properly[151].

In 1999 the Ludwig-Maximilian University in Germany reported cattle cloning experiments. One live and normal calf was born and three others aborted late or died after birth, showing abnormalities in the kidneys and liver and in one case "severe malformations of the legs" [17].

A US study published in *Theriogenology* in 1999 detailed the health of 13 cloned transgenic calves and foetuses, resulting from 110 embryos transferred into cows. Three of the 12 pregnant cows died during pregnancy, 5 foetuses were stillborn or aborted and 8 calves were liveborn (6 by Caesarean section). Three had difficulty breathing and one of these died from heart and lung failure after 4 days. Another died at 6 weeks with breathing problems and a "grossly dilated" heart. All the calves were given oxygen to aid survival [16].

Advanced Cell Technology, Massachusetts, put the genetic material of a dead gaur into the enucleated egg-cells of cows (using a total of 692 eggs in the experiment). Only 8 of 42 cows became pregnant and 7 either miscarried or were aborted because of problems. One gaur calf was born but died 48 hours after birth from an intestinal infection[154,155].

One of the most successful cattle cloning companies, Advanced Cell Technology, has published results on the health of 30 cloned Holstein cattle up to 4 years old in 2001. From 496 cloned embryos transferred into 247 hormonally synchronised cows, 110 cows became pregnant and 80 of these aborted. Six of the 30 calves died shortly after birth. The deaths were due to placental abnormalities and heart and lung failure. Several of the calves had high blood pressure and respiratory distress at birth[18].

The biotech company Immerge BioTherapeutics and the University of Missouri produced cloned miniature piglets with the α-1,3 galactosyl transferase gene deleted, in the autumn of 2001. Twenty eight surrogate sows were implanted with cloned embryos. Three sows, implanted with around 100 cloned embryos each, gave birth by caesarean section to 7 cloned 'knockout' piglets. Two piglets died shortly after birth from breathing problems and a third died after 17 days from heart failure. One of the surviving piglets, one had heart and lung abnormalities, one had eye and ear abnormalities and one had a leg joint abnormality. Of the dead piglets, 2 had leg problems and one had a cleft palate[19].

Health problems of clones. A group of 13 cloned transgenic calves and foetuses assessed at Texas A&M University 1997-1998. Source: J R Hill et al., Clinical and pathological features of cloned transgenic calves and fetuses (13 case studies), *Theriogenology* **51**:1451-1465 1999.

Foetus 1	Aborted at 8 months; lung abnormalities
Foetus 2	Stillborn; mother died in pregnancy; abnormal placenta; heart/lung abnormalities
Foetus 3	Stillborn; mother died in pregnancy; abnormal placenta; fluid in lung
Foetus 4	Stillborn; mother died in pregnancy; abnormal placenta; fluid in lung
Foetus 5	Stillborn; mother died in pregnancy; heart/lung abnormalities
Calf 1 (died at 4 days)	Abnormal placenta; Caesarian delivery (mother died); breathing difficulty; oxygen for 4 days; heart and lung failure
Calf 2	breathing difficulty; oxygen for 1 day
Calf 3	Caesarian delivery
Calf 4	Caesarian delivery, oxygen for 2 days, pneumonia
Calf 5	Caesarian delivery
Calf 6 (died at 6 weeks)	Abnormal placenta; Caesarian delivery; oxygen for 1 day; leg abnormality; pneumonia; heart failure
Calf 7	Caesarian delivery; breathing difficulty; oxygen for 1 day
Calf 8	Normal delivery

9.2.2 Clones in commercial farming

The examples in the previous section make it clear that it is unacceptable at this stage to consider the use of cloned animals in farming. There is abundant evidence that they are often not normal animals and could not survive normal farming conditions. The following are examples of unexplained deaths on farm reported during 2001.

California State University announced at the beginning of April 2001 that 3 cloned calves had been born on March 9th. The calves were moved to the University's farm to see how they would 'perform in a typical farm setting' and the result was that 2 died from a bacterial infection at less than one month old. "It is not uncommon for cloned animals to have problems with their immune systems", according to the University's agriculture faculty. An animal reproduction expert at Purdue University commented of cloned animals, "Almost all of these animals, if born on a farm without a vet hospital, they probably wouldn't survive". [156]

In June 2001 there was another unexplained cloned calf death in the US. A 9-month old Jersey calf, cloned from an adult cell, was found dead in her pasture at the University of Tennessee's Experiment Station. The head of the cloning project said, "We are basically clueless at the moment and mystified" [157,158].

Experts fear that even clones that look healthy could be "ticking timebombs", destined to go awry. Cloning experts in the US concluded a study of gene regulation in cloned mice by stating:

> "Our results indicate that even apparently healthy cloned animals can have gene expression abnormalities ….that may cause subtle physiological abnormalities which could be difficult to detect" [20].

Cloned animals may age prematurely. In 1999, the ends of Dolly's chromosomes (structures called 'telomeres') showed signs of greater wear than normal for her age[159,160]. She was cloned from a 6-year old ewe. In 2001 Dolly developed arthritis, which is unusual for a 5 year-old sheep and could be the result of cloning[21].

According to *New Scientist*, a leading UK scientist argues that companies need to carry out controlled farm trials to prove that large-scale farm cloning involves no cruelty and that clones are as healthy as normal animals and that their meat and milk is safe and nutritious [116]. Public information about the health of clones is essential for the assessment of animal welfare in cloning as well as the safety of cloned food, pharmaceutical products or animal organs. CIWF Trust is concerned that some biotech companies and research institutions may not be giving the public the full facts about the health of cloned animals.

9.3 Regulation of animal welfare

In 1998 the Farm Animal Welfare Council (FAWC) expressed concern about the oversized offspring produced by cloning and the waste of life involved in the high losses of embryos, foetuses and mature animals killed as part of the cloning procedure. The FAWC recommended a moratorium on the use of cloning in commercial agriculture until the problems had been resolved[7]. The Council also believed that there were potential problems from loss of genetic diversity or the introduction of deleterious genes into the gene pool, resulting in genetic abnormalities or susceptibility to disease. The recommendation to government was that this aspect of cloning should be controlled by legislation[7].

In the UK, experiments to produce GM or cloned farm animals are regulated in the same way as any other animal experiments. All experiments on farm animals are carried out under the Animals (Scientific Procedures) Act 1986, including breeding from GM animals. Genetically engineered animals "that can be demonstrated not to be prone to pain, suffering, distress or lasting harm as a result may be discharged from the controls of the 1986 Act", on the discretion of the Home Office[161].

There is no specific regulation at the moment to protect GM or cloned animals in a commercial setting, either in industry or conventional farming. There are many serious questions about the health and well-being of the animals, about their quality of life and housing - would containment be used, either for their protection or for environmental protection? - about invasive testing procedures carried out on them, about their ability to reproduce naturally. Would weak or unhealthy animals be kept alive by medical intervention, in order to produce valuable products such as semen, eggs or proteins? Meanwhile, there is a worrying lack of transparency from the companies that claim to have "production herds" of transgenic sheep or cattle about their levels of health, reproductive fitness and lifespan.

The UK expert advisory body, the Agriculture and Environment Biotechnology Commission (AEBC) believes there is a need for a review of all animal protection legislation in farming to deal with these types of issue[162]. CIWF Trust believes that the current decision-making process on farm animal genetic engineering and cloning is clearly inadequate and urgently needs to be reformed.

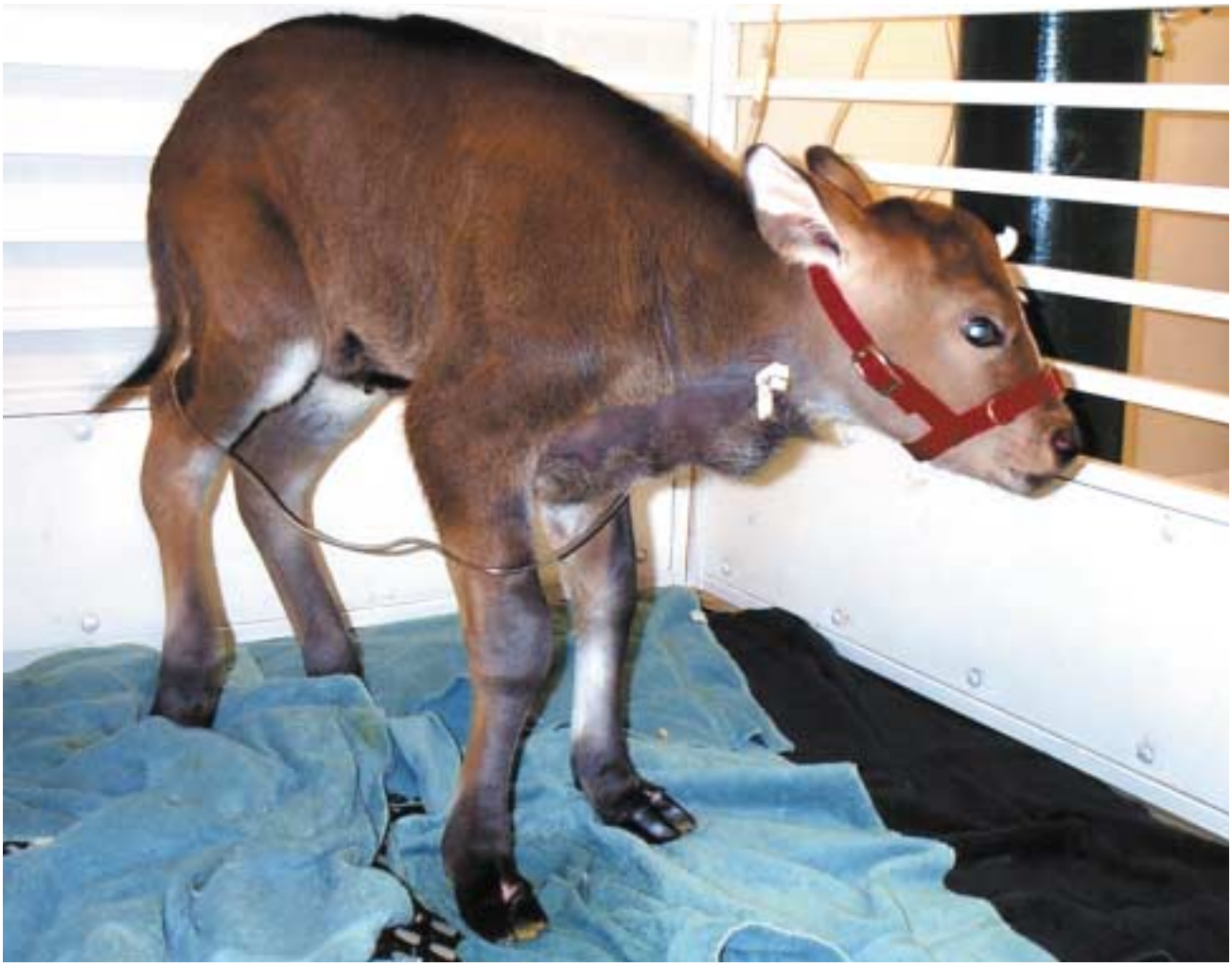


Figure 8: Noah, a gaur calf cloned by US biotech company Advanced Cell Technology, died of an infection 48 hours after his birth in January 2001. His surrogate mother, a cow, was the only one of 43 cows implanted with cloned gaur embryos to calve.

10.0 Consumer safety and environmental risks

The production and commercial use of GM animals present a number of potential problems and risks that are just beginning to be debated in public. The UK's Royal Society believes that GM animal products may be on sale to the public within 10 years[4,163]. The Society argues that before this happens, a number of potential risks must be investigated, including;

> "novel or increased allergic reactions (for GM animals used for food or feed); possible toxic effects (from the production of toxins or other biologically active proteins); adverse effects from a change in behaviour or in physical nature, e.g. increased aggression; changes in the ability of the animal to act as a human disease reservoir (e.g. the insertion of a novel viral receptor); and effects on the ecosystem of release of the GM animal into the environment"[4] [Section 5.2].

Concerns about GM animal farming

Environmental risks would be much increased by commercial, non-contained use of transgenic animals for food or non-food products. A single transgenic milking cow could produce 70 litres of potentially contaminated water a day in manure and urine.

The New Zealand Royal Commission on Genetic Modification was told of concerns over[49]:

- Consumption of milk and meat from genetically modified livestock
- Potential future uses of products derived from genetically modified livestock
- Any long term unanticipated health effects
- The disposal of large quantities of urine and faeces from transgenic animals even when kept in 'containment'. One suggestion is that risk would be minimised merely by "not overloading natural biological breakdown systems in the soil"[49]

10.1 Environmental hazards

> "The uncontrolled release of genetically modified animals into nature might trigger quite significant changes in some wild animal species that the majority of human beings wish to keep essentially in the present state." L M Houdebine, *Transgenic animals: generation and use* 1997[164]

Environmental hazards due to GM animals could be difficult to detect, to predict or to control. A review of risks by the French agricultural research institute (INRA) lists a catalogue of possible problems, requiring containment of GM animals, control of their reproduction and elimination and destruction of the animals at the end of experiments. This is necessary because "The mechanisms which control gene expression are so complex that some of the biological effects of a transgene cannot be predicted in most cases"[164].

The known or unknown presence of mobile DNA elements (such as viruses) used in genetic engineering is another serious risk, according to this expert. Even if the transgene put into an animal poses no danger to the animal or to other life, it "may contain known or unknown mobile elements or genes" which "may have deleterious effects and generate some biorisks". Examples are transgenes that code for toxins or that "modify the animals in such a way that they can become very dangerous in specific conditions ", such as containing genes coding for receptors of human or animal viruses, or, in xenotransplants, the risk of transfering prions (the infective agent for BSE and its human form) or even transgenes that generate new pathogens[164].

Even animals that appear to be experimental 'failures' and not to carry the transgene should not be treated as normal animals, since "They may be highly mosaic [i.e. they carry the transgene in some of their cells but not in others] and their transgene may have escaped detection". Animals that carry mobile foreign DNA or any foreign gene that is potentially dangerous for humans or the environment would need to be contained to prevent interaction between the animals and the environment, including barriers to insects, parasites or pathogens. All their waste and their bodies would need to be inactivated by autoclaving (high temperature treatment)[164].

In keeping with these risks, transgenic cows in New Zealand have been required to be kept in close containment. All genetically-modfied material, and the milk and waste products were to be kept on site or destroyed, so there would be negligible risk to the environment or public health[165]. In 2001 public protests in New Zealand resulted in the High Court ordering the slaughter of a small herd of cows carrying transgenic embryos[166].

10.2 Safety of GM animal products

Regulators may be contemplating allowing human consumption of animals that have undergone genetic engineering experiments. These might either be 'experimental failures' or animals used in the 'pharming' industry. In 1991 the US Department of Agriculture agreed that animals called "No-Takes" can enter the food supply if they test negative for a transgene and are healthy[167]. The UK's Advisory Committee on Novel Foods and Processes agreed in 1994 that it saw no problems in allowing 'experimental failures' used for human consumption[168]. A US Food and Drug Administration expert stated in 1997 that "it can be anticipated that sometimes it will be desired to salvage ['biopharm' animals] for food, thereby avoiding other more costly means of carcass disposition" and that consequently "Biopharm animals may well be the first transgenic animals to be offered as food for humans" [167].

Consumption of GM or cloned animal products raises a number of issues. According to the USDA veterinary experts, "Although it may be possible to 'turn off' the expression of the transgene, and therefore limit exposure to the expression product, it will not eliminate the transgene from the animal" [167]. However, "The standard battery of toxicology studies…are not appropriate for assessing the safety of a transgene in genetically modified animals" [167]. There would have to be tests for "unsafe residues of drugs and other chemicals that were used during the utilization of the animal as a protein factory…[which] may remain in portions of the animal that might be offered for food" [167]. Some scientists are relying on cooking or human digestive enzymes to inactivate any foreign DNA in meat[49]. In addition, testing for the transgene may be ineffective, if experimental animals are 'mosaic' (see above, Section 10.1).

All the evidence to date is that most consumers would not be prepared to eat genetically modified and cloned meat, milk and eggs. A MORI poll of British opinion sponsored by Novartis in 1999, found 74% were opposed to the cloning of animals and 71% were opposed to the genetic engineering of animals to produce "nutritionally improved food" [169]. The Eurobarometer survey published in December 2001 by the European Commission found that 70.9% of people questioned reject genetically modified food. 59.4% believed GMOs could have negative effects on the environment. 94.6% believed consumers should have the right to choose[170]. Some scientists believe that these attitudes are due to public ignorance and superstitious fears. But the survey found that "This is not true with GMOs. People interviewed could have a high level of knowledge and still believe that biotechnologies should be subject to more control and demand more safety studies etc." [170]

There is very little public information available on the long-term health of GM and cloned animals. But it is possible that subtle abnormalities in an animal could affect the safety of either food or pharmaceutical products derived from it. Tellingly, nearly 86% of people in the European survey wanted to know more about GM food before eating it [170]. In the case of farm animal products, public information would need to include a full chemical analysis together with detailed information on the animals' health and welfare.

10.3 Regulation of GM animal products

The UK has not yet approved the consumption of experimental animals. When a GM animal is killed it should be disposed of as with all other GMOs (under GMO (Contained Use) Regulations) and should not enter the food chain.

It is an offence to release any GMO into the environment without consent under the Genetically Modified Organisms (Deliberate Release) Regulations 1992 (as amended 1995 and 1997). Applications must include a full assessment of the impact on human health and safety and the environment and are reviewed by the appropriate environment, agriculture, health and safety authorities. Each application is reviewed also by the Advisory Committee on Releases to the Environment (ACRE). The FSA would decide on the safety of transgenic farm animals for consumption. This would need demonstration of the safety of: the transgene and any regulatory or additional parts; the expressed gene in the tissue or product; other consequences of transgene expression [161].

Some products may have an ambiguous status and could slip through the regulatory net. In 2000 the biotech company PPL was reported to have 20 cows producing human alpha-lactalbumin for use as a baby milk. As with other 'nutraceutical' products, there is room for confusion as to whether baby milk would be regulated as a food or have full pharmaceutical testing[77]. As nutraceuticals are a rapidly growing market, they may well form a large proportion of transgenic animal products in the future.

By 2001, no application has been made to release or market a GM animal in the EU[161]. CIWF Trust is concerned that the regulation worldwide is *ad hoc*, piecemeal and leaves the public open to risk from unforeseen effects of known or undetected transgenes and leaves the transgenic animals' welfare largely unprotected. There is an urgent need for a public review of the use of transgenic or experimental animals and their products for food.

10.3.1 Cloned meat and milk

Milk may be one of the first GM or cloned products to get authorisation for consumption.

But it is unclear how regulators would regard cloned animal products. Some have suggested that cloning would be regarded as equivalent to embryo transfer, if no engineering of DNA was involved. The US National Academy of Sciences is to prepare a report to assess the risks of cloning in farming to humans, to the environment and to animal welfare, expected in 2002. A senior regulatory scientist has been quoted as saying "There's a pretty good chance there won't be a need to regulate them"[171]. US cloning companies are now poised to sell cloned dairy cows into commercial farming for milk production. The biotech company Infigen is reportedly preparing an analysis to prove to the US FDA that milk from its cloned Holstein cows is normal and suitable for consumption[171].

In the UK, According to the UK Food Standards Agency (FSA), cloned meat and milk would be classed as novel foods and so would need a special licence, but unlike GM food would not need to be labelled[116]. Some cloning experts are worried that cloned animals may be less healthy than they originally seem. Food products from cloned animals with hard-to-detect health problems are a potential risk for consumers.

10.3.2 Experimental animals in the food chain

In practice, animals from biotechnology experiments have already entered the human food chain. In Tokyo a cut-price promotion of "cloned beef" has reportedly been held for the public, from one cow produced in Japan's cattle-cloning programme[172] and probably is sold more widely. In 2001 a University of Florida technician reportedly stole dead pigs, genetically engineered and injected with enough barbiturates and other chemicals to kill a 250 kg pig, and sold them to a butcher. The stolen pigs had been genetically engineered to develop a disorder similar to diabetes-related eye problems in people[173,174].

These few public disclosures are almost certainly the tip of an iceberg. If any of these experimental animals, some of them transgenic, carried viruses or other mobile genetic elements, the environment and human health may be already at risk from spread via human faeces and urine in the sewage and water systems.

10.4 GM-created pathogens?

Genetic engineering of animals, especially those in contact with humans, poses the risk of unintentional or intentional infection of humans with new pathogens. In the context of potential bioterrorism, these concerns should be taken all the more seriously. HIV, Anthrax and, probably, the Ebola virus, are human pathogens that originated in animals. Influenza pandemics are believed to arise from an exchange of genes between bird or pig viruses and human viruses[175].

Altered or mutated viruses could be lethal to humans and other animals. The risks of genetic engineering both for animals and potentially for people were vividly demonstrated when Australian scientists unintentionally made a normally harmless virus lethal to mice. They had engineered the virus (mousepox) to add a gene that they believed would be beneficial to the mice's immune systems. However, the gene disabled the mice's immune system and the virus killed them within days[176]. *New Scientist* commented, "Adding the gene turned a merely nasty virus into a killer"[177]. A combination of parts of the HIV and the Ebola viruses has reportedly been used experimentally on mice to insert a new gene[178] and a top UK university has produced a potentially deadly hybrid virus by combining genes from the Hepatitis C and the dengue fever viruses[179].

The UK's Royal Society had noted that genetic engineering could unintentionally create animals that are new hosts to diseases that could be passed to humans [4]. The potential of viruses to cross species and the effect they can have in a new host are illustrated by recent outbreaks of avian influenza, which killed 6 people in Hong Kong in 1997[180] and of pig encephalitis in South East Asia, which killed over 100 infected people between 1998 and 2000[181].

11.0 Safety and efficacy of xenotransplantation

The debate over xenotransplantation focuses on the two questions of whether it would be helpful for people with organ failure and whether it would be safe for those people and also for the population at large. A vital question that has not been acknowledged or answered, is whether animal organs would be capable of sustaining human life and health. A 1998 survey of research on the subject shows that there are significant biochemical and functional differences between animal and human organs, such as hearts, kidneys and livers. These species incompatibilities can only be tested when the first volunteer patients have animal organs implanted[182].

On the question of safety, there may be unexpected problems in using cloned pigs for xenotransplants, if it turns out that the animals age prematurely or have subtle abnormalities. This could affect the long-term effectiveness of the organ and the safety of the recipient. But the question that has so far raised the most public concern is the risk of virus transfer to the recipient and hence to the general population.

11.1 PERV

A major potential risk of using GM pigs for providing xenotranplant organs is that Porcine Endogenous Retroviruses (PERV) could inadvertently start a new viral epidemic among humans. Retroviruses incorporate themselves into the host animal's DNA, where they may be inactive before transfer to a new host. They are inherited from parents in the normal way. Researchers in France have found 11 types of PERV in pig organs, including heart, liver, pancreas and kidney[183]. At least 50 copies of PERV exist in pig chromosomes and cannot be eliminated by pathogen-free, closed breeding of the animals, according to a UK xenotransplant expert[184].

In 2000 and 2001 scientists reported evidence in the respected journals *Virology*, *Nature* and *Journal of Virology* that PERV from transplanted pig cells can infect other organisms and could infect and replicate in human tissue[185-187].

Numbers of respected scientists, including those who support xenotransplantion research, have pointed out the dangers. *New Scientist* reported a leading UK expert as asking, "Are we setting off a new epidemic? No-one has any idea. It's very unlikely. But so was HIV"[183]. Another commented, "If you know what the disease is you know how to look for it. It's possible there could be viruses we don't know about that could be released into the human population" [188]. There is also the possibility of hybrid pig-human viruses emerging through gene recombination in the cells of xenotransplant recipients[25].

Nature magazine, the mouthpiece of the UK scientific establishment, has also commented on the risks. In 2000 the magazine reminded readers that

> "Contagious viruses are a major worry in xenotransplantation, as they carry the risk of creating manmade pandemics".

An editorial warned, "The pathogenicity of animal viruses can also change unpredictably when they jump the species barrier" [189]. When, in the spring of 1999, the US Food and Drug Administration banned the use of primates as organ donors because of the

"significant infectious disease risk" to the public, the magazine advised, "It would be a mistake to conclude that the FDA's exclusion of primate donors means that other animals, such as pigs, are safe" [190]. In early 1999, the Council of Europe, representing 40 countries, called unanimously for a legally binding moratorium on transplanting animal cells, tissues and organs into human beings[191].

11.2 PERV-free pigs?

Companies who want to use pigs for xenotranplants argue that they will elininate PERV from the pigs they use, either by breeding or by genetic engineering [126,132]. But other scientists believe that this is "illusory"[183] or "impossible" [63]. A report in the *Journal of Virology* in 2001 concluded that it was not clear "if all potentially functional [PERV] proviruses [viruses integrated into the pig's genome] could be removed by breeding or whether gene knockout technology will be required to remove the residuum"[192].

11.3 Views of the UK's regulatory authority

The UK's Xenotransplantation Interim Regulatory Authority (UKXIRA) has considered the public health steps that would be necessary if "xenotranplantation gave rise to a demonstrable emergency such as the emergence of a highly infectious disease". If that happened, UKXIRA says it would be feasible to pass rapid emergency legislation to allow "compulsory removal to, and detention in, hospital of such people [i.e. patients and contacts]" [193]. But, according to a US expert in transplant infectious diseases, PERV infection would be hard to detect in people who had been given xenotransplants because pig cells would be circulating in their bodies; "we can't tell directly whether or not there is infection by PERV of host tissue when there are pig cells floating around".[194]

The UKXIRA's 3rd Annual Report in 2001 concluded that xenotransplant experiments had not proved that the transplanted animal organs could sustain life in humans and neither had rejection problems been overcome. The authority's opinion was that, "the likelihood of whole organ xenotransplantation (particularly for heart transplants) being available within a clinically worthwhile timeframe may be starting to recede"[29]. It suggested that alternatives such as heart assist devices and tissue engineering could show promise. The risk of viral transfer was still a "major concern", concluded the UKXIRA. Any person who received a xenotransplant would have to undergo lifetime surveillance and use barrier contraception, because a "single cell, or a single viral particle, may present an infectious risk" [29].

12.0 GM animal feed

Feed for intensively farmed animals takes up a considerable proportion of the world's crops. At least one third of the world's cereal crop goes into animal feed, around 95% of the soya crop and 70% of the maize crop[195]. This huge market for non-human feed has been the major target of biotech companies producing GM crops for farming. By 1999 it was estimated that up to 50% of the soya and maize crop worldwide was genetically modified, mainly for herbicide resistance. In late 2001 the European Commission was reported to be planning to resume its approval process for commercial planting of GM crops, halted since 1998[196].

Feed is also being genetically engineered to include special nutrients and so increase farm animals' growth rate. CSIRO in Australia increased wool growth by 8% and live weight gain by 7% by feeding sheep GM lupins containing the gene for a sulphur-containing protein[197].

12.1 Implications for consumers

The potential risks to human health from GM animal feed come from the possibility of increasing antibiotic resistance and from risks to people consuming the transgene in animal products. Antibiotic resistance genes from bacteria are used in GM crops, for example as 'markers'. Antibiotic resistance, a major threat to human and animal health, can be transferred between bacteria through gene transfer and in some circumstances bacteria can transfer genes to mammalian cells[198]. A House of Lords Select Committee has concluded, "it is certain that gene transfer between micro-organisms takes place"[199] and noted the concern that there is a "remote but finite possibility that the gene could be transferred to bacteria within the rumen of a cow" [199].

There is already evidence that parts of transgenes from GM feed could be eaten by people. There are conflicting results from studies about whether fragments of foreign DNA, such as in Bt-maize, can be detected in chickens. However, a 2001 report in *European Food Research and Technology* found that short DNA fragments from plants used in feed could be detected in white blood cells of cows that had been fed GM maize and in milk. Plant DNA fragments were also detected in muscle, liver, spleen and kidney of chickens (although specific DNA from the transgene itself was not detected in the chickens or the cows)[200]. A study by the UK's Advisory Committee on Animal Feedingstuffs concluded that, "The results indicate that DNA fragments large enough to contain potentially functional genes survived processing in many of the samples studied"[201].

12.2 Implications for farm animals

GM crops are a potential risk to farm animal health. Animals are being fed GM crops that are not considered acceptable for human use. The UK government admitted that GM crops from its controversial field trials might be fed to animals. The GM StarLink maize (corn), which the US FDA does not allow in human food because of inadequate testing and fears of allergic reactions, is already approved as feed for animals[202].

Some evidence already exists that animal health could have been damaged. GM potatoes appear to have had unexpected effects on the gastrointestinal tract of rats[203]. Twice as many broiler chickens reportedly died when being fed a GM maize (Chardon LL) than when being fed normal maize in an industry trial[204].

CIWF Trust is very concerned that farm animals are being given GM feed without adequate evidence of its safety. Animals should not be used as a sales outlet for agricultural products or by-products that cannot be sold elsewhere. When this was done in the 1980s (when mammalian meat and bone meal was fed to herbivorous cows and sheep) it proved a serious mistake. Farm animals should have access to nutritious food appropriate to their species as an important part of maintaining animal health.

13.0 Do we need GM and cloned farm animals?

> "These technologies and the livestock produced will have a significant impact on agriculture, livestock production, medicine and society as a whole" .
>
> L'Huillier, *Proceedings of the New Zealand Grasslands Association*, 1999[205]

Advocates of farm animal biotechnology claim that it could bring us a range of benefits in more efficient farming and pharmaceutical production, as well as possible health benefits to the animals themselves. Some even expect that the new animal biotechnologies will revolutionise animal farming. But there is an equal possibility that, far from being a revolutionary way forward for farming, genetic engineering and cloning are taking us back to a further intensification of our use of farm animals and a degradation of our relationship with them.

13.1 Farming for food

Farmers have been promised gains in efficiency. They have been told that these could be achieved by genetically engineering or cloning animals that are more productive and cost-effective, are more consistent, are more resistant to diseases or could yield more desirable or novel products.

Attractive as these claims sound commercially, they are often much exaggerated. The current level of knowledge means that only single genes can be changed. As experts at the Roslin Institute and elsewhere[206,76] have pointed out,

> "commercial traits are physiologically complex, controlled by several genes of medium/small effect" [206].

At the present, we do not even have a detailed knowledge of animal genomes, or the function of the genes. We do not understand the genetic factors controlling so-called production traits. We do not understand how gene expression is normally controlled in different body tissues and organs. In sum, according to the UK's Royal Society, "Many of the desirable traits such as disease resistance and production traits are polygenic and require the alteration and coordinated expression of several genes, many of which have yet to be defined"[4] [Para. 72]. Nor, indeed, do we understand how cloning and genetic manipulation could affect the long-term health of the animals and how this could affect consumers.

13.1.1 Faster growth and higher yield

According to its advocates, biotechnology could be used to make farm animals grow faster and consume relatively less feed. The Royal Society says that "An important agricultural goal is to introduce desirable alterations in growth rates or feed conversion efficiency. Yet another is change in the composition of meat to produce either leaner meat or to enhance anti-microbial properties of milk for newborn animals"[4] [Para133].

Yet from the point of view of animal welfare, it is very hard to see how genetic engineering to increase growth and yield can be justified at all. We have seen in Section 2.1 the stress put on the animals by selective breeding for ever faster growth or higher yield. Treating farm animals as units of production, at lowest cost, cannot in the long term be consistent with acceptable animal welfare standards.

The health and welfare of farm animals has already been damaged by excessive specialisation caused by selective breeding. Using genetic engineering to increase the growth rate of broiler chickens, or increase the milk yield of dairy cows, must be seen as a very retrograde step from the point of view both of animal health and, equally, the public perception of farming.

Dairy cow with enlarged udder

BST Bovine Somatotrophin (BST) is a growth hormone that can be manufactured by genetic engineering and injected into cows to increase their milk yield. It may increase milk yield by 10-20%. BST directs nutrients away from other body tissues towards the udder – it therefore extends the period of catabolic stress (when tissue is broken down) for milk synthesis after calving. Although used for around 30% of dairy cows in the US, the use of BST is illegal in the EU, confirmed in 2000. The Farm Animal Welfare Council stated in 1994 that "BST can have severe effects on welfare, particularly in relation to the occurrence of mastitis and other diseases… various reports exist suggesting increased lameness and other production-related diseases, impaired conception and tender injection sites". [207] In 1997 FAWC re-iterated, "the use of BST is unacceptable on welfare grounds". [208,209] The European ban followed recommendations confirming the scientific evidence against BST from Health Canada (1999), the European Scientific Committee on Animal Health and Animal Welfare (1999), and the UK's Veterinary Products Committee, among others, and lobbying by environmental and animal welfare organisations, including CIWF. Some also believe that BST-derived milk could be a health risk for humans.

13.1.2 Cloning for replication of high-yielding animals

Some biotechnologists advocate cloning to reproduce high-yielding farm animals, such as dairy cows. At the moment the extreme 'inefficiency' of cloning means that it would be not economic to try to clone less valuable animals – but in the future, if the method ever became routine, it could be used to produce large numbers of nearly identical sheep, pigs and chickens bred to meet market specifications.

Cloning will always involve unnecessary suffering. At the moment, for cows, the proportion of embryos that result in cloned calves is still only 1/3 of that of IVF[5]. Even if scientists managed to get pregnancy rates for cloned embryos similar to those from conventional embryo transfer (around 50%), for example, the egg-donors and parent animals would still have to undergo invasive and painful procedures. The use of superovulation and embryo transfer have taken us far from natural reproduction, in order to maximise output from our farm animals. Cloning would take us much farther in this misguided direction.

Cloning is very likely to damage genetic diversity. Already, without cloning, selective breeding and reproductive technology (such as artificial insemination and embryo transfer) has reduced the gene pool for farm animals. The UK's Farm Animal Welfare Council has concluded that, "no regulations exist to prevent inbreeding as AI operates in a free market and the farmer is free to purchase any semen he may choose"[7]. In fact, inbreeding in commercial dairy farming, encouraged by AI and ET methods, has gone so far that it has been predicted that by 2015 the US Holstein cow population will be so inter-related that it is equivalent to only 66 unrelated individuals[210].

As a result of our intensive breeding policies, "erosion of biodiversity at the breed level is not simply a concern for the distant future, but of immediate concern", according to a global study of farm animals and the environment published in 1996[210]. In developed countries over a fifth of breeds are at risk of extinction and "Market forces are causing much of the diversity problems in the OECD countries"[210] .

Cloning risks introducing deleterious genes very rapidly to hundreds of thousands of animals by mistake. The FAWC pointed out that "any tendency to lose genetic diversity may make it difficult or even impossible to reverse the effect of such deleterious genes once recognised. Without some form of control, the narrowing down of the genetic pool could occur relatively quickly"[7]. CIWF Trust believes that cloning as a method of reproducing farm animals is a continuation of a misguided and largely discredited selective breeding policy and would lead animal husbandry further into intensification.

13.1.3 Disease resistance

Infectious animal diseases cause large financial losses to farmers and some also cause suffering to the animals. The Royal Society suggests genetic engineering could be used against a number of infectious diseases, such as Marek's disease, a devastating viral disease of chickens that causes wasting, blindness and paralysis; the Maedi-Visna virus of sheep and goats worldwide causing pneumonia, arthritis and encephalitis; scrapie and BSE in sheep and cattle; and trypanosomiasis, transmitted by the tsetse fly among cattle in Africa[4].

These are all serious problems, but it is far from clear that genetic engineering is the answer. Current selective breeding, for example of dairy cows, broiler chickens and pigs, has probably already increased rather than decreased disease risk (Section 2.1). We have created herds and flocks that are genetically so similar that a single pathogen could infect the majority of individuals. Such animals would also be highly susceptible to a bioterrorism attack.

Many farm animal experts, including organic farmers, believe that diseases would be better

tackled by research into husbandry and breeding methods that promote animal health. Breeding for multiple traits in Nordic countries, including health and fertility, have shown an overall economic benefit. Studies suggest that selective breeding for mastitis resistance would be effective and profitable because it would reduce costs of veterinary treatment and the culling of sick cows[2]. Similarly, scrapie is a rare sheep disease which affects many but not all European countries and is not found in New Zealand and Australia. Because scrapie may hide BSE in sheep, it is now seen as urgent to breed scrapie susceptibility out of sheep in the UK and elsewhere. Selective breeding is likely to be a more effective and cost-effective solution than many years of genetic engineering experiments.

CIWF Trust believes that the most important contribution to animal health and welfare is to reform intensive farming, rather than to create GM disease-resistant farm animals. As *New Scientist* magazine commented in 2001;

> "why are animal diseases such a problem in countries like Britain anyway? The answer lies less in the DNA of our cows and pigs and more in our subsidised system of intensive farming and long-distance trading in animals which encourages infections. There is a danger that genetic modification will be used to shore up this system by making farm animals better equipped to survive cramped conditions. Indirectly, it could even help to spread disease susceptibility by encouraging farmers to switch from genetically diverse breeds to high-yield GM animals drawn from a narrow gene pool." [211]

13.1.4 Engineering animal behaviour

Intensive farming practices often frustrate the natural behaviour of animals and their need for exploration and social contact. But some biotechnologists suggest that animals could be genetically engineered so that their intelligence and behavioural needs were reduced.

The Canadian Expert Panel on Husbandry of Animals Derived from Biotechnology has considered two such ways of fitting animals to current farming systems. One is to cause the death of all male chick embryos of egg-laying strains, to achieve "elimination of the need for the post-hatching sexing of chickens and the euthanasia of males". The second is to produce chickens that have lost their usually strong motivation to dustbathe, thus suiting them to intensive housing. The Panel suggests, "The presence or absence of a particular behaviour in a bio-engineered animal may not of itself trigger a concern for animal wellness" [212].

Should we consider behavioural engineering of farm animals ethical? An animal science expert from the University of Utrecht has commented,

> "At present, the tools for selection and genetic modification have drastically changed. From an ethical point of view it is questionable whether these new techniques can be used for creating animals which, eventually, will be deprived of their present natural physiological and/or behavioural needs (and changed into creatures that can be kept under impoverished environmental conditions), without compromising their well-being"[213].

13.1.5 GM animals and developing countries

Advocates of animal biotechnology argue that one of the main benefits of farm animal genetic engineering would be for developing countries. The Royal Society suggests that genes for resistance to trypanosomiasis found naturally in the N'Dama breed of cattle in sub-Saharan Africa could be put into high production dairy cows such as Friesians[4], for use in Africa.

There are both economic and ecological flaws in this approach. It is highly unlikely that the average small farmer in developing countries could afford to buy genetically engineered or cloned animals, as the Royal Society itself admits. If it happened that high-yielding GM or cloned farm animals became available to large farmers or to multinational companies engaged in farming, this would be more likely to result in displacing and ruining small farmers.

There is danger in exporting the genetics of Western highly selected farm animals to developing countries, whether by genetic engineering, cloning or conventional selective breeding. The potential for greater productivity of the imported breed must be balanced against the problems. Imported breeds are likely to increase farmers' dependence on high inputs. Indigenous breeds are "highly adapted to the rigorous environments in which they [are] expected to produce", according to a global study of farm animals sponsored by the European Commission (EC), FAO and World Bank[210]. They are adapted to harsh climates and to parasites and can forage for food. Western high-yield farm animals are likely to incur costs for housing, machinery and veterinary care and they may suffer if these are not provided. They have been selectively bred to eat high protein, high energy feed. Without this type of feed they often cannot continue to give high yields.

The EC study concluded that

> "over the long term most exotic breeds have not been able to maintain high levels of productivity" [210].

The export of Western farm animal genetics already threatens the genetic diversity of the world's farm animals. 37% of the 582 world cattle breeds for which population data exist are either at risk or projected to be at risk, together with 46% of pig breeds and about 30% of sheep and goat breeds[210].

13.1.6 Unfit farm animals

The majority of good farmers want their animals to be healthy. But it is possible that highly productive but unhealthy transgenic animals could be attractive to some farmers.

If farmers wished to use GM animals that would suffer unless they were given special treatment, such as regular pain relief, the farmers could be legally obliged to provide it. The report of an expert panel on Husbandry of Animals derived from Biotechnology in Canada[212] has concluded that this requirement would be hard to enforce. The Panel concludes: "Mitigation strategies essential for the management of animal pain and distress arising directly or indirectly from the bio-engineering and which import significant human and economic costs are at risk for non-compliance". They recommend that these animals should not be used in general commercial agriculture, but, alarmingly, they believe, "They may however be suitable for controlled and selective release"[212] [Para. 14].

CIWF Trust is appalled that any regulatory authority should consider authorising the farming of unfit GM or cloned animals.

13.1.7 Biotechnology and the cheap food policy

Producing meat, milk and eggs faster and more cheaply is still put forward as a goal for farming.

This is in spite of the fact that the cheap food policy has been shown to be self-defeating for many farmers, discredited with consumers, and highly damaging to animal welfare. Genetic engineering and cloning should be seen as part of this mistaken policy.

If genetic engineering and cloning became a viable technology, it is possible that genetically engineered or cloned animals could increase some farmers' profits. The EC's Ethical, Legal and Social Aspects project on the future of farm animal breeding expects that, if European agriculture were to take the "low cost path" followed by producers such as the USA, South East Asia and Canada in the global market, cloned and transgenic animals would be likely to be used in Europe[214].

But it is more likely that genetic engineering and cloning would damage farmers' livelihoods. Small farmers would be unlikely to be able to afford the technology and its use could accelerate the trend visible in the UK, the US and now the developing world, towards fewer, bigger and more industrialised farms. The Dairy Science Department at Virginia Polytechnic, for example, believes that

> "the prospect of creating cows that produce specialised milk may have momentous consequences for the structure of the dairy industry"[74].

This is a prediction that might well concern small and traditional dairy farmers.

Even if genetic engineering and cloning led to successful cost reduction, a cheap food policy is unlikely to provide a successful future for European farming in a global market. Egg production costs are already considerably lower in the USA, for example, and imported US dried and liquid egg products could compete with European eggs when battery cages become illegal in the EU in 2012, according to a 2001 report by the RSPCA. A successful alternative approach is taken by Switzerland, where battery cages are already illegal. Financial support is given to Swiss farmers to cover the extra costs of non-cage systems[215]. CIWF Trust supports the EU's proposal that payments to farmers to offset the costs of improved animal welfare should be included in the 'Green Box' of payments that do not encourage additional production, established under the World Trade Organisation (WTO) Agreement on Agriculture.

It is increasingly clear to both European farmers and politicians that a high-welfare policy is in the interests of both farmers and consumers. The Dutch Agriculture Minister has recently written in a wide-ranging policy review that there is need for a "turnaround in thinking and action" on animal welfare in farming and that animal health and welfare should be "the basis of new husbandry and breeding systems". These systems would need support from consumers, retailers and government, with tax and other incentives[216]. CIWF Trust believes that WTO rules should allow any country to refuse to import animal products that come from systems that do not meet that country's own legal animal welfare standards.

13.2 Pharming proteins

Advocates of 'pharming' argue that it can produce benefits for human medicine and health, that it will use only a fraction of the animals used in agriculture, and that the animals will be so valuable that they will be well cared for and healthy. CIWF Trust believes, on the contrary, that the history of pharming to date amounts to an unacceptable intensification of our use of farm animals. There is a real danger that pharming could become the new intensive farming at the very time that consumers are looking for more natural and animal-friendly methods of food production.

13.2.1 Creating the production herds

It has been estimated that 3 products currently in development would need to use 4300 transgenic sheep to meet market demand for AAT, 5400 transgenic cows to produce human serum albumin and 4 transgenic pigs to produce Factor IX [8]. But a much large number of experimental and breeding animals would be needed to create these production herds. According to the UK's Royal Society in 2001, "the efficiency of genetic modification of the farm animal genome is low (less than 1% of GM offspring in pigs, sheep, goats and cattle)"[4]. Only around 10% of offspring born are transgenic [5], or fewer. In a recent experiment to produce cloned transgenic sheep carrying the human AAT gene, 227 ewes were used to create 3 healthy transgenic lambs[10].

Pharming companies are under pressure to build up large transgenic herds or flocks rapidly for commercial-scale production. As well as conventional breeding technology such as superovulation and embryo transfer, cloning would probably be used. In the present state of cloning technology, as many as 10 - 80 adult animals could be used for each healthy offspring that was produced. Hundreds of thousands of sheep could be used to build up a milking flock of 4000 ewes. Wastage of animals on this scale would be considered unethical by the majority of people, especially if the same product could be achieved by any other method.

13.2.2 Pharming unlimited

It is unrealistic to believe that because the number of products made in transgenic animals is relatively small at the present, only few and high value animals will be used in pharmaceutical protein production. Proteins are legion and highly varied molecules that have applications throughout and beyond the bioscience industries. Over 1000 biopharmaceuticals were in clinical trials by 1998[140]. Numerous potential targets for antibodies are being discovered. Pharming companies already want to produce antibodies to use as additives in toothpaste, against mouth bacteria that cause tooth decay[28]. If 'pharming' were to become accepted as a production method, it could spawn a wide range of marketable goods.

Not only human proteins, but non-human foreign proteins could be made in transgenic animals. We have already seen 'spider-silk', a new material potentially useful in a wide range of industries, made in goat's milk. Commercial logic would operate in the same way with animal 'protein factories' as it does with cars or washing machines, to create more, different and cheaper goods in a competitive commercial environment. If farm animals are seen as living chemical factories, there could be no limit to the genetic modifications that could be attempted on the tissues of their bodies.

The distinction between 'pharming' and farming for food production is artificial and is likely to break down in the future. Biotechnology companies are already experimenting with 'nutraceuticals' produced from transgenic animals and it is highly likely that if transgenic manufacturing becomes established it will spill over into farming for food. The numbers of animals used in pharming could rise even above the numbers used in conventional farming. As the technology becomes routine, and the value of the animals decreases, there is no reason to think that 'pharm' animals will be treated with greater consideration than animals in food production. In addition, there will be continuous genetic experimentation on farm animals in the search for new products.

13.2.3 Safety and acceptability of pharming

> "[T]he risk of prion transmission in trangenically produced therapeutics …is one of the most serious concerns voiced by regulatory agencies"
> *Genetic Engineering News* 1.4.2000[140]

The public is generally less concerned and critical about the production of pharmaceuticals than about the production of food. Our diet can usually be a matter of choice, whereas people generally have little choice about medicines. Consumers increasingly want to know how their food was produced, which is not yet the case for pharmaceuticals. Biotechnology companies are aware of this difference in attitude and some, like the Roslin Institute, have decided to concentrate their efforts on transgenic production of pharmaceuticals rather than food. CIWF Trust is very concerned that biotechnology companies are now using pharming as the route to develop their research into transgenic animals, until such time as the public is ready to accept GM animal food. CIWF Trust believes that the public has the right to know the animal welfare issues involved in pharming, including details of the lifespan, management, health and output of pharmed animals, in the same way as this information is available openly for animals used in farming.

Will pharmed products be acceptable on safety grounds? Pharmaceuticals and nutraceuticals produced in the cells of transgenic farm animals have the potential to transfer pathogens, such as prions (associated with BSE and scrapie) and viruses, to humans. The USDA has established guidelines for the maintenance of pathogen-free herds[26]. The biotech company PPL has shown its concern by using sheep from New Zealand, where scrapie is not found. At least two companies are creating 'knock-out' sheep and cattle which lack the prion protein gene[24]. As of Spring 2001, the US FDA had not approved any 'pharmed' products. Hygiene and purification problems remain. According to an industry analyst, public acceptance of transgenic proteins "may be dependent on the public's perception of their hazard. It is unfortunate that much of the public perceives that transgenics are unregulated" [137].

13.2.4 Animal welfare in mass production

From the point of view of animal welfare, pharming raises many of the same issues as farming for food. It is very likely that the animals used as 'bioreactors' will be over-specialised for one function and for high yield, in the same way as has happened in intensive farming for food. This is perhaps even more likely in pharming, if the animals are kept in containment out of the sight of the public.

The search for new products for nutrition, medicine and industrial materials is likely to lead to unsuitable proteins being produced in the udder, at least experimentally, causing painful damage to the udder and possibly other organs, if proteins are made in urine and semen. Some of the products that are tried out may be toxic to the animals. Animals producing proteins in urine may be permanently tethered, as already happens to pregnant mares used for hormone production. Animals producing protein in blood or semen could be subjected to frequent bleeding or 'milking'. All production animals are likely to be subjected to frequent blood and tissue tests for quality and biological safety control. A major concern is how these animals will be housed and managed. The demands of biosecurity, to avoid transmissible diseases, are likely to mean that these herds of identical transgenic animals will never see

the open air and will be subjected to sterile and barren conditions. The mass-produced protein industry could become the new factory farm.

13.2.5 Human health needs

The usefulness of pharmaceuticals produced in transgenic animals has yet to be proved. But there is no question of the importance of finding solutions to the health problems they hope to address. CIWF Trust believes that these solutions should also include research and action programmes on the causes and prevention of disease and on positive health promotion.

The importance of the health problems should not prevent us from questioning the decision-making process which had led to widespread genetic experimentation on farm animals and the plans for their use as 'bioreactors'. There are proven alternative methods of producing most of the pharmaceuticals where transgenic production is being tried, including the use of bacteria, mammalian cells and transgenic plants. Often the main reason for attempting to use animals is a possible cost reduction in the future. CIWF Trust believes that our society needs to debate the issue of cost in the context of medical priorities and medical spending as a whole, taking into account the very large welfare cost to the animals in the pursuit of the transgenic production technology.

In the case of xenotransplants, there are many reasons to doubt that animal organs will work well in humans[182]. The UK's xenotranplantation regulator concluded in 2001, "Survival times in animal (primate) models do not yet provide substantive data that xenotransplanted organs are capable of sustaining life in humans"[29]. Even if they did, the potential benefits of xenotransplants have to be weighed against enormous risk. A UK expert writing in *Science* reminds us that

> "The possibility remains that, say, one among 1000 xenograft recipients may become infected by PERV or by a virus resulting from recombination between PERV and human retroviral sequences….It took more than 20 years for HIV-1 to spread out of Africa, and it is only after 55 years of individual benefit from antibiotics that we are facing the public health threat of multi-drug resistant microbes"[184].

13.3 Human ethics and farm animal biotechnology

Farm animal biotechnology, like intensive farming itself, raises fundamental ethical questions[217]. The prime question in this context is, do we have a right to genetically engineer farm animals?

The answer to this will depend on one's view of the nature and intrinsic value of the human being as opposed to the animal being. Western society – and indeed most human societies – have awarded primacy to the human, that is, to ourselves. And religion has played a key role in promoting and maintaining our distinct status for the human. Catholicism allots a soul to the human but not to the animal, and the whole Judaeo-Christian tradition holds that animals exist as an aid and benefit to humans, which we have a right to use – and, possibly, a duty to care for[217]. This was re-iterated in 2001 in a report from the Pontifical Academy of Life, which argued that humans enjoy a unique and superior dignity which means that research into transgenic animals is "morally acceptable" if there is "relevant benefit for humans"[218].

This majority religious tradition has totally permeated western culture. The survival of these views in a post-Darwinist society is a serious anomaly. If modern biology has taught us anything, it is surely that humans and non-human animals are extraordinarily similar, both genetically and physically, and also emotionally[217]. As Darwin explained: "man and the higher animals, especially the primates, have some few instincts in common. All have the same senses, intuitions, and sensations, similar passions, affections and emotions…they feel wonder and curiosity…they possess the same faculties of imitation, attention, deliberation, choice, memory, imagination, the association of ideas, and reason though in very different degrees"[219].

If we award intrinsic value to human beings, as we do, then it is hard to see how we can make a good case for not awarding intrinsic value to animals. Our similarities at every level so obviously outweigh our differences. Already our society is moving forward on this issue. In 1997 the EU Member States added a legally-binding protocol to the European Treaty of Amsterdam, recognising that animals are "sentient beings", a landmark recognition of the fact that they can feel pain and can suffer[217]. Farm animals are sentient beings, with intelligence and complex social and family behaviour. Scientists are contributing to this understanding; recent research has shown that "individual sheep can remember 50 other different sheep faces for over 2 years" and that their memory of sheep and human faces lasts "after long periods of separation"[220]. And if we agree that animals have intrinsic value, it is hard to argue that we have the moral right to genetically engineer them.

How can we make balanced decisions about our uses of farm animals? As society is gradually rejecting the religious tradition of human primacy and supremacy, we are left with an inadequate ethical tool-kit to justify our actions. Often our justification comes down to historical precedent – we have always done it – or belief in our own intellectual superiority[217]. Our usual cost-benefit assessments, that form the basis of regulatory decisions, are rooted in our traditional assumptions and take the primacy of human benefits for granted. Better frameworks for ethical decision-making, such as using an 'Ethical Matrix' to take account of all the interest groups involved, including the animals, are now being developed[221,222]. CIWF Trust believes that there is an urgent need for review and reform of our ethical decision-making process in relation to farm animal biotechnology.

14.0 Conclusions and recommendations

At the beginning of the new millennium, at a time of crisis in farming and animal health, there is a widespread recognition by farmers and consumers that intensive agriculture is unsustainable and must give way to high-welfare animal husbandry. This report has shown that genetic engineering and cloning are part and parcel of our mistaken pursuit of intensification in our use of farm animals. These biotechnologies should not be part of the future of animal farming in which health and welfare should be priorities.

Over the last half century, the excessive use of selective breeding and the application of reproductive technologies have increased the production of cheap food, but , as our report shows, they have reduced farm animal genetic diversity and damaged animal health and welfare. Farm animals are now being genetically engineered and cloned in the search for ever cheaper food, pharmaceuticals and novel foods and materials. The experiments are being done with a totally inadequate understanding of the underlying science and the possible consequences, either for the animals, or the long-term consequences for humans and our ecosystems. Meanwhile, as our report details, the hit-or-miss experiments have caused enormous animal suffering and waste of animal lives.

CIWF Trust believes that the following steps are now urgent:

- **A moratorium on all experimental and commercial use of GM or cloned farm animals, whether for food production, pharming or xenotransplantation, until scientists have a better understanding of the basic science of genetic engineering and cloning. CIWF Trust believes that this is the only way to halt the current widespread suffering of farm animals subjected to these technologies**
- **Reversal of our present selective breeding practices in favour of breeding for improved animal health and welfare, together with the promotion of dual-purpose and slower-growing breeds.**
- **Re-direction of research effort and funding away from farm animal biotechnology and towards commercially acceptable farming and breeding methods that promote animal health and welfare**
- **Provision of public information on the health, management, lifespan and output of GM and cloned farm animals, in the same detail as is available for animals in conventional farming**
- **Establishment of an Animal Welfare Committee, including biotechnology as part of its remit, to advise government on ethical matters regarding all uses of farm animals**
- **Establishment of an Animal Ethics Committee (a) to consider fundamental questions regarding society's relationship with and use of animals, and (b) to promote discussion and debate of such issues**

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