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Cloning animals

Summary

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SUMMARY

The TA project »Potential and risks of the development and use of cloning and of genetic engineering and reproduction technology in breeding animals for research, in breeding laboratory animals and breeding productive livestock« is based on an application by the Bündnis 90/Die Grünen parliamentary group in the German Parliament (Bundestag pub. 13/7160). With the aim of improving the information basis TAB was to be commissioned to make an inventory of this complex and ethically-charged issue. The TA project »Cloning animals« was adopted in summer 1997 by the Committee for Education, Science, Research, Technology and Technology Assessment of the German Parliament, and started at the beginning of 1998. The goal of the project was to study

> what influences the use of nucleus transfer cloning may have on biological fundamental research,
> what contributions can be expected for the various application-oriented areas of medicine,
> what impacts are evident for animal breeding and agriculture,
> and finally, which problem areas can be identified and what conclusions can be drawn.

Even during concept elaboration it became clear that restricting consideration to purely technical, medical and economic aspects of the use of cloning in animals would be unsatisfactory. Consideration of the legal and ethical aspects of cloning is also required. The report accordingly addresses the question what regulations (if any) animal cloning is subject to in Germany under current legislation and whether cloning may be subject to statutory restrictions or even prohibitions. In view of the possibilities the further development of cloning techniques may have in terms of possible human areas of application (drugs, transplants, tissue culture etc), it also seemed necessary to consider the actions of doctors, biotechnologists and animal breeders in the context of scientific and technological advances and ethical demands. The ethical question posed was whether conventional ethical principles, classic arguments and relevant models of ethical evaluation are adequate for the moral evaluation of cloning.

The following sections review the most important results of the study for the individual issues and conclusions.

THE FUNDAMENTALS: CLONING PROCEDURES

A clone is an individual which is genetically identical with another individual. Cloning is a form of asexual reproduction which is widespread in nature. In the case of single-cell organisms and plants, it is an entirely normal process (division, vegetative reproduction), in the case of the higher vertebrates genetically identical individuals can arise naturally through the spontaneous division of embryos in the early stages of division, with the parts evolving separately into independent individuals (twins, multiple births).

There are in principle two procedures for artificial cloning of higher organisms: embryo splitting, and cloning through nucleus transplantation to egg cells or embryo cells whose genetic material has been removed (nucleus transfer). Cloning techniques come under biotechnology, specifically the (biotechnology) procedures which do not modify the genetic material in the cell nucleus. Cloning techniques are, however, generally applied not in isolation but in combination with other biotechnology and genetic engineering techniques (transgenic, which modify genetic material). Here, many biotechnological procedures are an essential element of cloning, while others are optional.

Embryo splitting and nucleus transfer differ fundamentally in terms of the technique and the degree of genetic identity achieved in the resulting embryos. Embryo splitting changes neither the age nor the (toti-)potency of the cells used. The (two) embryos from the splitting are in the same stage of development, exactly the same age as the undivided embryo would have been and genetically completely identical. The nucleus transfer technique of cloning takes a different approach by transferring the genetic program (the cell nucleus with the desired genetic material) from a totipotent blastomer or no longer totipotent cell (embryonic, foetal or even a differentiated body cell) to an unfertilised egg cell whose nucleus has previously been removed. This technique basically offers the possibility of replicating an adult individual and their genetic program. The result is a new individual whose existence does not derive from the fertilisation of an egg cell by a sperm cell.

The surprising thing of the cloning technique that resulted in Dolly in 1997 is that a mammal egg cell to which a nucleus from a differentiated body cell is transferred can develop into a complete organism. The genetic material in the cell nucleus of a differentiated body cell is functionally differentiated and modified in many ways compared to the genetic material in the cell nucleus of a fertilised egg. Previously it had been assumed that cell nuclei from differentiated or specialised body cells could not in principle be reprogrammed to develop again

into an individual. The Dolly experiment has accordingly raised the problem of the need to redefine the totipotency of a cell (the developmental potential to differentiate into any type of cell and tissue).

In principle there are highly promising prospects in the application of cloning, both for biomedical fundamental research and for agriculture, particularly in combination with transgenic techniques. However, before we reach the point where applications are relevant – and, above all, efficient – a series of important questions have to be resolved. Cloning based on nucleus transfer has not always succeeded or been successful in the long term. Many of the embryos created in this way die, not infrequently shortly before or after birth. However, the surviving animals also frequently have »deficits« which hamper their development and have a deleterious effect on their health. Today, we do not know yet in detail what the sources are for the errors which currently prevent cloning based on nucleus transfer from being efficient. The mechanisms for differential gene activation in normal reproductive and developmental processes are certainly still too little understood. The question remains what the differences are between natural development processes and those occurring after artificial nucleus transfer.

BIOMEDICAL RESEARCH AND APPLICATION

Clones of higher organisms are of great interest for biomedical fundamental research and applied medical research. Currently, four possible areas of application of cloning based on nucleus transfer are basically under discussion for medical purposes.

Animals as drug producers

The first area is so-called »gene pharming«, i.e. the use of transgenic animals to manufacture (human) proteins with therapeutic use, e.g. in their milk. This is one of the possible main areas of application in the foreseeable future for cloning based on nucleus transfer, as this makes creating the transgenic animals more effective and specific compared with conventional techniques. The advantages of the active ingredients from biogenetic manufacturing processes (such as insulin, blood factors or other human bodily substances) are that they can be obtained in much purer form than with conventional techniques involving animal and human intermediate products. Given the availability of such animals, production of active ingredients can be on a large scale and relatively cheap. However, there are also risks to the animals due to the genetic (transgenic) manipulation, the biological activity of the produced protein and the cloning procedure itself.

Hazards to people can arise from changes in the products and possible transmission of disease (pathogens), and these have to be avoided as far as possible by careful testing of drugs.

Animal models

Another area where cloning could be used is producing transgenic animals as animal models for human diseases. Animal models are used to study the biochemical and physiological fundamental processes, and provide valuable information for understanding these in humans, and naturally also on human diseases and possible therapies. Further, new drugs can be tested in animal models for their toxicity and pharmacological effect on humans. A major obstacle in developing animal models has been that so far we have only succeeded in the case of the mouse in integrating genetically manipulated cells into the germ track of a recipient animal so that the genetic changes can be passed on. However, the physiological and anatomical differences between mice and humans are so great that symptoms of the genetic changes induced in the mouse often do not match the symptoms observed in humans.

Cloning using nucleus transfer and somatic cells creates the possibility of inducing specific genetic changes in various species (gene targeting and gene knockout). This would also make it possible for the first time to induce disease in transgenic large animals which could be superior to the former mouse models in terms of anatomical, physiological or genetic characteristics (depending on the disease to be studied). It is generally expected that this will contribute in the medium term to an improved understanding of the clinical picture of genetically-caused human diseases, and developing effective therapies based on this. Possibilities for research and implementation in this area should accordingly be specifically encouraged and promoted.

Breeding endogenic body tissue

Cloning could also make a technical contribution to the transplantation of endogenic (autologous) tissue and in so-called cell therapy. The ideal transplant tissue is easy to identify. Its cells should be as genetically identical as possible with those of the recipient. The patient's immune system then no longer recognises them as alien, eliminating problems of rejection. One optimal solution would accordingly be creating genetically identical replacement tissue. Research findings indicate that this could be done through cloning using nucleus transfer.

There is another approach to breeding human replacement tissue which is conceivable in principle. This involves using the nucleus transfer technique to create an early embryo from which pluripotent embryonal stem cells can be obtained in vitro. In humans, however, it has not yet been possible to obtain such cells even from embryos in vitro. Such a technique would also require the ethically and legally highly questionable creation and utilisation of a human embryo, unless egg cells from animals are used as recipients for the nucleus. However, this development is still in its infancy and involves its own problems, and specifically difficult ethical questions.

Xenotransplantation

A fourth area in which the use of (transgenic) cloned animals is conceivable is xenotransplantation (transplanting animal organs into humans). However, to create »donor animals«, up to a dozen genes would have to be modified in the pig, for example. This is effectively impossible using conventional techniques of genetic modification. Cloning could now make it possible to make the desired genetic modifications to cells in vitro before cloning them using nucleus transfer to make an animal with multiple genetic modifications. Even if the »ideal« donor animal could be made in this way, however, the basic problems of rejection would probably remain. It is also not certain that the alien animal organ will actually perform its function in the human recipient. This also leaves the problem of animal viruses adapting to humans, with the possible consequence of epidemics (cf. TAB 1999).

LIVESTOCK BREEDING AND AGRICULTURE

Biotechnological techniques have been in use for some time in animal breeding and animal production. This development dates back over 50 years to the introduction of artificial insemination. The breeding possibilities of artificial insemination quickly took on great significance (in Bavaria, for example, c. 90% of cows and 60% of sows are artificially inseminated). Progress in breeding is, however, limited (especially in cattle) by the fact that a cow can only bear one calf a year. Embryo transfer offers the opportunity here of obtaining ten and more offspring from valuable cows in a single year. Embryo transfer is now used extensively for cattle. Other biotechnological methods, e.g. in vitro fertilisation, gender diagnosis or selection, gene diagnostics and gene transfer, are expected to lead to great advances in animal breeding if they can be applied without side effects, cost-effectively and ready for practice.

Cloning itself is not a breeding technique, but one which makes possible genetically-identical replication of individuals. Cloning alone does not involve any breeding or genetic advance in the resulting clones, compared to the original individual. The decisive factors in the economic efficiency and expediency of cloning for animal breeding in agriculture are the effectiveness of the cloning technique and the (breeding) value of the genetic material available for cloning. If techniques for cloning adult animals can be developed into a routine procedure, this would also have implications for animal production, whose extent would largely be decided by the cost of cloning. As long as the procedure is still very expensive, only isolated and extremely valuable, top-performance animals will be cloned, e. g. in the event of the loss (from age or disease) of the services of a very valuable breeding animal, it could be replaced by a clone of itself.

Transgenic clones

The expected increase in genetic knowledge of productive animals as well as the associated possibilities for creating transgenic animals combined with cloning using nucleus transfer make possible the use of new strategies in animal breeding and production. It is expected that these technologies will also make the »production« of transgenic animals with modified (agricultural) characteristics more efficient than currently possible. The most important goals for gene transfer in livestock breeding in combination with cloning are: quality enhancement, gene pharming, boosting resistance to disease, and cost reduction.

Enhanced performance through gene transfer is no longer as important nowadays in agricultural livestock, as the characteristics responsible for meat and milk production are complex and multigene, difficult to modify and also adequately handled by conventional breeding. In part, gene transfer is used in an effort to improve feed conversion or reduce fat formation, particularly in pigs. This, for example, is one aspect of the primary targets for quality improvement in animal products, as is the desired change in the composition of milk. Work is underway on increasing the protein content (specifically casein) and reducing or entirely removing lactose. This type of milk would also be tolerable for people who are lactose intolerant. Extending this approach leads to the gene pharming described above. Due to the high disease-related costs of animal factory farming, genetic modification of disease resistance in animals has great importance in animal breeding. Transferring specific disease resistance genes or deactivating sites on genes which determine specific diseases could improve animal health and hence (theoretically) the quality of animal products.

Changes to agricultural structures

In agricultural breeding practice the introduction of (practicable) cloning (particularly in cattle breeding) could result in a restructuring of breeding organisation. Cost considerations together with the requirements for employee qualifications would probably lead to the emergence of specialist, capital-intensive, commercially-oriented breeding companies. It is doubtful whether existing breeder associations will be able to perform the biotechnological work efficiently. Further, extensive use of cloning can be expected to lead to changes at the level of stages of production, with differing impact depending on the type and size of farm. This could reinforce the structural change in this sector and generally lead to a reduction in the number of farms and jobs in agriculture.

The possibility cannot be ruled out that the impact of cloning on the use pattern in agricultural land will reinforce the trends in the agricultural sector which have been evident since the 60s. The complete exploitation of all possible improvements in productivity by highly intensive and industrial-style operations leads to declining prices and – besides the reduction in area needed per animal – to further reduction in agricultural land while at the same time the number of livestock production farms and regions is increasing. Even in the highly competition-oriented livestock production regions, an increase in regional environmental pollution can accordingly be expected.

LEGAL ASPECTS

Among the legal aspects a particularly significant question to answer is which regulations govern animal cloning in Germany (and abroad) and under what conditions cloning is legally permitted or not permitted.

Animal testing – breeding for unhealthy traits

There is no explicit consideration of cloning technologies in the Animal Protection Act. However, cloning animals could be covered by the provisions of section 7 (1) of the Act (TierSchG), as this includes regulations on animal testing and cloning procedures are still overwhelmingly in the testing stage. The application and implications of this section are, however, debated in widely differing terms. If the removal of the nucleus from the egg is not regarded as modification of genetic material in the legal sense, the transfer of the egg to the brood animal does not constitute animal testing either. However, if one hold's the view (like e. g. the Federal Ministry of Agriculture and others) that cloning using nucleus transfer is

covered by section 7 (1) sentence 2 TierSchG because this involves manipulation of genetic material and cloning tests for genetically modified animals (or brood animals) may involve pain or injury, this would make cloning tests using nucleus transfer clearly subject to approval. Cloning animals could also and specifically be restricted by section 11b TierSchG (breeding for unhealthy traits) at the point where the techniques are ready for practical application and are, for example, used in producing and breeding farm animals. This would, however, only apply where cloning was used to induce unhealthy changes in the animals which were retained in subsequent breeding.

The current legal consensus seems to be that sections 7 and 11b of the Animal Protection Act constitute statutory regulation of cloning to the extent that this could involve suffering, pain or injury for the animals. A ban on cloning would, however, only come into question if significant suffering on the part of the animals is actually demonstrable.

Violation of constitutional rights

Constitutionally speaking, a ban on cloning would violate the constitutional rights of researchers and professionals under Article 5 (3) (Freedom of research) and Article 12 (1) (Freedom of occupation) of the German Constitution. A ban or other limitation on cloning would also constitute interference with the constitutionally-guaranteed academic/scientific freedom. There is no evident barrier within the constitution which could justify such an intervention. Under Art. 12 (1) of the German Constitution a ban on cloning would accordingly be unconstitutional as it is irreconcilable with the public welfare and not covered by the statutory reservation of Art. 12 (1) sentence 2.

Under current conditions, cloning animals is according permissible in principle and subject only conditionally to restrictions under prevailing law.

Inclusion of animal protection in the Constitution

A new situation could arise if animal protection was adopted as a state goal in the Constitution. A comparison with other countries shows that constitutionally-guaranteed animal protection currently only exists in Switzerland. Animal protection acquires constitutional status there at federal level through the concept of the »dignity of creatures« (Art. 24 amendment para. 3) and sets for example a barrier to the constitutional right of freedom of research. In Germany a draft constitutional article on these lines is currently being debated. The Bundesrat (Upper House) approved on 28.11.1997 draft legislation in the 13th

Bundestag (Lower House) amending the constitution by introducing animal protection as a state goal.

The Bundesrat motion aimed at adding an Article 20b to the German Constitution with the object of »respecting animals as fellow creatures and protecting them within the statutory framework against avoidable suffering and injury«. Animal protection here is mostly understood as limiting animal testing, but also with respect to factory farming, animal transport and animal slaughter. The Bundestag debated this motion without reaching a decision. A final decision is now a matter for the current (14th) legislature. If such an Article is incorporated in the Constitution, cloning animals could possibly violate a constitutionally-protected object, animal protection, as there could be an inherent constitutional barrier to Article 5 (3). It can at least be said, however, that under a constitutional guarantee of animal protection the necessary consideration of other constitutionally protected objects (such as freedom of research, academic/scientific freedom – but also freedom of occupation and guarantee of the right of property) could be achieved in an individual case of application of the law and a court ruling. Animal protection as a state goal does not rule out the use of animals by humans, but raises the requirements for the necessary justification of this use.

ETHICAL ASPECTS

The legal and legal-ethical considerations are associated with ethical considerations of fellow-creature status and an ethical judgement on animal cloning. Different positions in the social debate and assessment of animal cloning can be traced back to some extent to different fundamental values. These also determine whether animal cloning is seen as having a new quality compared with conventional animal breeding or with other new techniques in animal breeding as well. For some theologically-based positions, cloning is e.g. an interference with creation which humans have no right to undertake. Anyone who feels that animals have »intrinsic value« or »creature dignity« will generally regard cloning as morally dubious, at least. From an anthropocentric position there is above all the question of the safety of products made with the help of cloning techniques and the potential risks and hazards – ecological (reducing genetic diversity) and social (industrial mass production, concentration of capital, new dependencies). Other positions see animal cloning more as a catalyst which could further reinforce other undesired trends which are currently apparent and which result from the use of other biotechnological and genetic engineering reproductive techniques, rather than as a qualitatively new step in reproductive technology.

The different social positions represent an effort to attract support for a specific moral or ethical ideal and so possibly influence the political climate as well. Given the difficulty of reaching a moral consensus, it is necessary to consider which ethical principles a possible use of animal cloning needs to orient itself by. This means not only that a possible use of animal cloning needs to be ethically justified, but also abandoning the use of the (therapeutic) possibilities offered by this technique. In this context the focus in ethical assessment of cloning is the question whether goals of animal cloning and the means or techniques used imply interference with the sphere of interests of the animals involved, and if in this case the interference can be ethically justified in terms of the considerations described above.

Specialists in ethics generally regard the goals of biomedical research and application as paramount, with special urgency or even literally vital importance for human health, and attainable only with the help of cloning of higher animals. Goals in fundamental research can also be regarded as paramount and justifying cloning higher animals where no alternative techniques are available. However, if cloning involves considerable suffering for the animal involved, it is necessary to consider whether mere human thirst for knowledge is adequate justification, or whether justification requires specific goals, i.e. the need to avoid considerable human suffering. Goals which are regarded as subordinate in importance to the above objectives are mostly goals in livestock breeding, where these do not explicitly involve ensuring the basic human food supply.

CONCLUSION

In applied research, cloning using nucleus transfer opens up new approaches to creating transgenic animals. Some proteins with therapeutic effect can be cheaply produced in this way. Obtaining autologous replacement tissue seems particularly promising in both medical and ethical terms, and the associated research is accordingly particularly deserving of promotion. It is not clear whether it will be possible to create better test models for human diseases in livestock, but the considerable medical importance justifies increased effort and support in this area as well. Overall there appear to be a relatively high potential benefits for research and medicine from cloning using nucleus transfer.

In agriculture the (practicable) production of clones of breeding stock promises to improve animal performance and quality while simultaneously reducing production costs. It is likely that cloning techniques will add further weight to existing trends in optimising the performance potential of livestock, i.e. high-per-

formance animals. With regard to the questions of genetic improvement and diversity in animal breeding, selection for specific performance characteristics can have the goal of standardising (breeding) livestock with the help of cloning, and hence inevitably standardising livestock generally. The resulting (desired) genetic status quo is accordingly very probably tied to a reduction in genetic diversity. Although there is in principle still great need for research on more exact documentation of the status quo, appropriate measures should be taken now to limit »artificial« production of increasing numbers of offspring of individual animals. This relates to techniques ranging from current routine artificial insemination through to cloning.

It is also likely that the introduction of cloning in combination with other reproductive and genetic breeding techniques will lead to or intensify extensive relocation of breeding products (breeding animals) from farms to commercial companies. This would result in a situation in animal breeding which is similar to that in plant breeding, where there is an inverted pyramid based on a few breeding companies, with a large number of propagating firms and numerous production firms. The pressure on the responsible EU organs and national governments to create a favourable environment for the commercial use of genetic and cloning technologies will probably increase. This includes for example demands to abolish so-called »competition-distorting regulations« such as quotas and ceilings on promotional measures or stocks. The consequences of possible further encouragement to this trend, which has been apparent in agriculture since the 70s, are not only quantitative but also qualitative. It would be important for policy-makers to ensure that a situation does not arise where the possible adverse effects of specialisation in animal breeding at the various levels of breeding, the labour market and farm structure are exacerbated or may even become irreversible. Overall, the application of cloning using nucleus transfer in agriculture requires careful consideration of the advantages and disadvantages. As far as the quantity and quality of human food is concerned, there is no direct need to clone animals for agricultural use. In addition, the currently foreseeable effects on the individual farm animal – and also on populations (breeding stock), breeds and possibly even species – are perhaps at least as serious as the impact on agricultural structures and the socio-economic conditions for people working in agriculture.

In ethical terms, an assessment of animal cloning must in principle be based on the same criteria which are (or should be) used in traditional animal breeding. In this respect there are various calls for the creation of a national ethics commission to deal with the moral and ethical issues of advances in biological and biomedical technology generally and with the consequences of advances in non-hu-

man biology and medicine. Its task would be to advise policy decision-makers and inform and educate the public. Possibly, intensive cooperation in the human area may be desirable with a national ethics commission which is also under discussion, and under certain circumstances a single ethics commission dealing with the entire human and non-human area of scientific and technological developments in biology and biomedicine may be meaningful. As broad groups of the public are also concerned about the use of cloning techniques with humans, the implementation of participative processes is important in opinion forming and policy advice (such as consensus conferences or citzens' fora). The need for forward looking and timely consideration and possibly legislation on cloning in humans cannot be lightly dismissed. Analysis of the legal aspects of animal cloning showed that this is currently legally permissible and subject to only limited restrictions under present legislation. In principle the question of animal protection is partly in contradiction to the actual goals of the Animal Protection Act in Germany at the present time, and in principle animal protection is secondary to the constitutionally-guaranteed freedom of research.

A different point of view and resulting implications could arise if the Constitution is amended to incorporate animal protection as a state goal. Constitutionally-based animal protection would presumably have relatively great practical effects. Such a provision would force the courts to strike a balance continuously between opposing constitutional rights and state goals. Developments in the field of cloning could in principle demonstrate the need to give animal protection constitutional status, or even the need for a fundamental debate in politics and society generally on the (current) treatment of animals in research and agriculture.

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