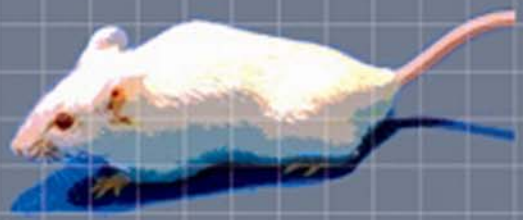
Man or mouse?

Etchical aspects of chimaera research

REPORT



THE DANISH COUNCIL OF ETHICS

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Preface

Chimaeras are living organisms incorporating cells from at least two different individuals. For a number of decades researchers have been developing chimaeras by moving cells – and whole organs – from one individual to another. A famous example of a profound chimaera is the sheep-goat (the "geep") created by a group of researchers that included the Danish researcher Steen Willadsen in the mid-1980s. In the case of a human-animal chimaera it involves an animal that contains human cells or a human that contains animal cells. It is not least within stem cell research that use has so far been made of certain types of human-animal chimaeras.

With the creation of human-animal chimaeras, research compels us to pose questions of one of the conditions of life we have hitherto taken for granted. We normally think of animals and human beings as two distinctly discrete categories, and the borderline between humans and animals is fundamental to our culture and legislation. Human beings are covered by far more comprehensive protective considerations than animals, which among other things can be made part of medical experiments associated with certain risks, be put down, kept as pets and eaten. Virtually no country, including Denmark, has legislation covering creatures that are not either animals or human beings.

Will chimaera research be capable of producing crossbreeds that cannot be classified as either animals or humans? Could we end up with individuals we would not know how to treat?

Although that potential scenario presumably lies a good way off in the future yet, the Ethical Council for Animals and the Council of Ethics consider that the research calls for an ethical discussion and decision on the extent to which the production of crossbreeds will be ethically problematic. What kind of human

characteristics justify the special status we occupy in the animal kingdom? When will an individual have been modified in some ethically meaningful way, and will parts of chimaera research be able to result in the production of such significant crossbreeds and – not least – how can the legislation take into account the latest research and prevent the creation of ethically problematic crossbreeds?

In order to identify these issues, the two councils therefore set up a joint working party in spring 2006 consisting of, from the Ethical Council for Animals: Karsten Vig Jensen and Peter Sandøe, and from the Council of Ethics: Peder Agger, Klavs Birkholm, Klemens Kappel, Ole Hartling, Thomas G. Jensen, Niels Jørgen Langkilde and Peter Øhrstrøm. Thomas G. Jensen and Peter Sandøe acted as chairmen for the group.

The councils wish to thank a number of people for having made their knowledge available to the Council's and the working party's work along the way. These are: Professor Outi Hovatta, a consultant from the Department of Clinical Science, Intervention and Technology at Karolinska Institutet, Professor Jens Zimmer Rasmussen, from the Institute of Medical Biology/Anatomy and Neurobiology at the University of Southern Denmark, Professor Poul Maddox-Hyttel from the Department of Basic Animal and Veterinary Sciences/Anatomy and Cell Biology at the University of Copenhagen, Ernst-Martin Fuchtbauer, associate professor from the Department of Molecular Biology at Aarhus University, Principal Scientist Palle Serup from the Hagedorn Research Institute, Professor Peter Arctander from the Institute of Molecular Biology at the University of Copenhagen, Peter K.A. Jensen, consultant, from the Department of Clinical Genetics at Aarhus Hospital, Professor Eske Willerslev from the Institute of Biology, Department of Evolutionary Biology at the University of Copenhagen, senior researcher Rikke Bagger Jørgensen from Risø National Laboratory and Mette Hartlev, professor from the Faculty of Law at the University of Copenhagen.

Anne Lykkeskov, MA, from the Council of Ethics' secretariat has been project manager and secretary to the working party, and together with Ulla Hybel, MA

(Law), PhD, has drafted the manuscript on the basis of the discussions on the working party and the councils. Thomas Mikkelsen, MSc, PhD, has written the appendix on chimaera research for the councils.

The working party handed over the report to the councils in spring 2007, and following consideration on the two councils it was finalized at a joint meeting on 21 June 2007.

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Chapter 1
Why engage in chimaera research? Ethical demarcation of the subject of this report

Chimaeras are the term for a group of distinctive cartilaginous fish, consisting of some 30 species that live in deep water. They are also called ghost sharks or rabbitfish on account of their partial resemblance to these creatures. But for the majority of people who associate anything with the word ”chimaera”, it is a creature that belongs to the realm of Greek mythology – a monster with three heads: a lion at the front, a goat in the middle and a serpent at the rear. The term chimaera, however, is also used of crossbreeds between humans and animals, for instance the sphinx, which the Egyptians represented as a creature with a woman’s head, a woman’s chest and a lion’s body. Many other peoples have also entertained tales of human-animal crossbreeds, and in our culture such creatures occur in science fiction and children’s books, for example.

Chimaeras, however, are not just deep-sea fish or fantastic creatures. Researchers have actually been creating chimaeras for several decades, in a different sense of the word, by moving cells – and whole organs – from one species to another. Thus, more than twenty years ago, a team of researchers with the participation of the Danish researcher Steen Willadsen created the so-called “geep” by mixing cells from very early goat and sheep blastocysts at the point when these had only developed to the 4 to 8-cell stage. The sheep-goat was sheep in some places and goat in some places—not a uniform mixture of sheep and goat. For example, it has a kind of patchwork hide, which in some areas was curly like a sheep’s and in others had wiry hair like a goat’s.[1]

But a chimaera need not be a dramatic mixture like those mythological creatures. The term is also used of an individual that has had at least one whole cell added

from another organism – an animal or a human being. Strictly speaking, a chimaera is a creature that has several different genomes, located side by side within the organism. That means that there are lots of chimaeras around us all the time. Everyone who has had a blood transfusion is – for a time at least – a chimaera, and mothers can seen be chimaeras, because they can contain cells from the fetuses they have borne, within them.

Taken to its extreme, then, the definition used in science means that being a chimaera need not per se have any ethical implications at all. But it might, for instance, if the transfer of cells affects the function of some of the organs we normally regard as identifying. Some of the experiments being conducted today could potentially assume such consequences.

Research thus has the potential to bring forth entirely new types of creatures, which can differ from the species we currently know in profound respects.

The Council of Ethics and the Ethical Council for Animals find that the research calls for an ethical discussion and decision as to whether the creation of crossbreeds will be ethically problematic. In this report the focus will be specifically on crossbreeds that in critical ways traverse the barrier between human and animal.

Obviously we have no body of experience as to how we should treat such ”transboundary” or ”crossover” entities, were they one day to be produced. For example, Danish legislation addresses *either* human beings *or* animals. The councils therefore wish to survey the existing legislation as well and point out areas that are being challenged by current or future types of hybrid and chimaera research.

[1] Fehilly, C.B. et al. (1984).

Ethical demarcation and possible ethical considerations

Chimaerization concerns mixtures between different animals and animal species, in particular, but the focus here is specifically on mixtures of animals and humans. This is due to the fact that the boundary between humans and animals is fundamental to tradition and to all common forms of legislation, as is also shown by the following examples of broadly accepted ethical and legal differences between humans and animals (in Chapter 3 there follows a more exhaustive description of the legislative differences):

Examples of how ethical and legal dividing lines between humans and animals have traditionally been perceived:

Animals	**Humans**
Not legal subjects	Legal subjects
Can be owned by others	Cannot be owned by others
No claim to respect for self-determination	Respect for self-determination
Generally allowed to be killed and eaten	May neither be killed nor eaten
Means	End in themselves

Of course, it is debatable whether these differences all bear closer discussion. But there is no reasonably doubting that they are basic building blocks of existing morals and legislation. That alone is one reason to discuss limits on chimaera research.

Not any form of chimaera is ethically interesting in this context. Not, for example, if it merely involves a person having a few animal cells added, but otherwise remaining human on the grounds of all the other criteria, or if something similar happens to an animal that has human cells added.

Therefore, we shall further confine ourselves to examining only mixtures between animals and human beings that might give rise to particular ethical problems:

1. Animal-human crossbreeds that undergo extensive modifications to what is perceived as identity-bearing characteristics, primarily the cognitive ones.
2. Animal-human crossbreeds so extensive that there may be doubt as to whether they belong to one species or another, including organisms that produce germ cells – and hence, in theory, offspring – of some species other than their own.
3. For some members of the councils, also animal-human crossbreeds that have otherwise had essential species characteristics modified will fall into the group that could give rise to ethical problems. This might involve, say, humans to whom animal characteristics are added for ornamental purposes.

In the following review of the different types of crossbreeds the focus will be on research with the forms of cross-boundary nature listed.

It should be mentioned that there are ways other than by producing human-animal chimaeras that mixtures of animals and human beings could conceivably come about that might give rise to the particular ethical problems mentioned. Here we are thinking of so-called transgenic animals, where animals are ”humanized” by inserting genes of human origin into the animal’s genome.

Since research into transgenic animals is a very extensive and wide-ranging sphere, however, the councils have chosen not to encompass in the present report. The councils will consider the issue of transgenic animals in a separate report. In this context, however, the councils would urge politicians—in as far as the development of transgenic animals leads to the kind of identity changes mentioned—to initiate the same reflections in terms of regulation as for chimaeric and hybrid crossbreeds.

Following the review of the research, an ethical analysis will be presented that discusses the way in which the research outlined may give rise to ethical misgivings.

Chapter 2
What chimaera research is being conducted?

For several decades researchers have been creating chimaeras by moving cells – and whole organs – from one individual to another, for example from animals to humans or vice versa. Over the past 20 years articles have been published in which researchers – particularly as part of stem cell research – have been experimenting with mixing cells from different individuals to make chimaeras.

The focus of the following review of ongoing hybrid and chimaera research will be on mixtures between animals and human beings[2]--research that will have the potential to produce organisms that have been modified in ways that may be ethically problematic.

No clear-cut answer can be given as to why research is being done into human-animal chimaeras, as this research is part of a number of different contexts. What is common to this research in altogether general terms is that its purpose is to increase our knowledge of basic biological questions (including stem cell biology) and eventually develop new treatments for diseases to benefit people suffering from disorders in which cells, tissues or organs of the body are degraded. A massive part of chimaera and hybrid research thus aims to investigate processes that can lead to cancer. For the sake of clarity it may be appropriate to categorize these trials and experiments according to some primary purpose, because the likelihood of creating the type of organisms we have defined as ethically problematic may be greater in the case of some types of experiment than others, partly depending on the purpose of the experiment. This applies, for example, where the *objective* is to create an animal with maximally humanized identifying organs.

For the same reason it may be expedient to distinguish between chimaeras

[2] The review is based on the appendix of the Report.

formed by supplying foreign cells to an individual after birth, and embryonic or fetal chimaeras, where the foreign cells are added while the individual is an embryo or fetus. In some cases the latter chimaeras can result in very far-reaching crossbreeds. In most instances, transplanting cells after birth does not give the transplanted cells an opportunity to develop, spread and differentiate to the same extent as when transplanting to an embryo or fetus.

Although some overlap will be involved between the categories in practice, we shall attempt to classify the research in animal-human crossbreeds under four main aims:

1. Basic or pure research
2. Creation of disease models
3. Development of new therapies
4. Research into reproduction and propagation

Basic research

The bulk of hybrid and chimaera research is basic research, which is particularly linked to stem cell research[3] and to characterisation of the function and potential of different cells. Different types of basic research can be distinguished:

Production of stem cells

Using the technique known as somatic nuclear transplantation[4], embryonic stem cells are produced by removing the nucleus from a specialized cell and inserting it into an egg cell that has been emptied of its own nucleus (enucleated). With the aid of the right culturing conditions and electrical stimulation, it has proved

[3] Stem cells are nonspecialized cells, two types normally being distinguished: *embryonic stem cells*, found in the early phases of the fertilized egg, the embryo, which can develop into *all* the types of cell of which the body is comprised, and *somatic stem cells*, found in the body's organs, which are more specialized but can still develop into a number of different cell types in the body.

[4] The technique used in somatic cloning, which came to be known when Dolly the cloned sheep was publicized.

possible to reset the cell nucleus, so that the result is blastocysts (early embryos) whose cells begin to divide. As far as is known, the technique has not yet been successfully made to work on human eggs.[5] One of the constraints on this development is the lack of accessible eggs from women, who need to undergo a course of not unproblematic hormone treatment to be able to donate eggs for research. That is why greater interest has begun to emerge in using egg cells from animals for nuclear transplantation, because such egg cells are more readily accessible.

In 2003 Chen et al.[6] reported having produced hybrid embryos by reprogramming cell nuclei from human connective tissue cells in ”enucleated” egg cells from rabbits. The embryos divided and developed to the blastocyst stage, following which the researchers took out stem cells that were pluripotent, i.e. able to develop into different specialized cell types. In the same way, in 2006, Illmensee et al. reported having reprogrammed human cell nuclei in bovine eggs and developed hybrid embryos, which developed to the blastocyst stage.[7]

The aim of these experiments is not to create crossbreeds, the desire being to develop stem cells that are maximally human. Nevertheless, in a way, they will be hybrid organisms, since a few percent of the resulting embryo’s gene pool will come from the animal cell’s mitochondria, which have their own (small) genome.

Testing the plasticity of stem cells

An important part of stem cell research involves testing the different cells’ so-called plasticity, which is to say their ability to develop into different cell types in the organism. One way of testing this plasticity is to add a marker to the cells, enabling them to be relocated later and then insert them into an animal embryo or fetus. If the cells display great plasticity, they will integrate into several different organs as the animal gradually develops.

[5] Personal communication with Professor Outi Hovatta, Karolinska Institutet in Stockholm.
[6] Chen, Y. et al. (2003).
[7] Illmensee, K. et al. (2006).

Here, again, ideally speaking, the optimal situation would be to carry out this type of experiment on human beings instead of animals. But most people consider it unethical to carry out this kind of experiment on human embryos, and in Denmark it would be out-and-out prohibited. Under the Danish Assisted Reproduction Act, fertilized eggs may only be kept alive outside of a woman's womb for a fortnight, from the time fertilization has taken place; only after that does actual organ development take place. In principle, this type of experiment could be carried out using born human beings (children or adults) as trial subjects, but this would require a large number of other conditions to be met, including prior safety studies (on experimental animals) and the possibility of a therapeutically beneficial profit from managing a particular disease.

In some experiments, adult human stem cells are inserted into early animal fetuses, where they are integrated into many organs and will make up a relatively small part of the individual organ. For example, in 2001, Almeida-Porada et al. described how, in this way, specific stem cells taken from adult human bone marrow developed into both haematopoietic cells, liver cells and skin cells following transplantation to sheep fetuses.[8]

In another type of experiment, non-specialized human embryonic stem cells are transplanted to specific organs in distantly related animals to see how they integrate into the organ. In 2005, for example, Moutri et al. transplanted human embryonic stem cells to the ventricles of the brain (fluid-filled cavities) in fortnight-old mouse fetuses in order to investigate the cells' capacity for differentiation.[9] As the mice developed, the cells became integrated in different parts of the brain, and the human cells formed connections with the mice's own brain cells and functioned like normal neurons. Moutri et al. estimated that less than 0.1% of the brain cells in the chimaera mice are human in origin. Incidentally, having chimaeric brains seemed to have no bearing on the mice. As

[8] Almeida-Porada, G. et al. (2001).
[9] Moutri, A.R. et al. (2005).

the ”architecture” – size and design – of the mouse brain is very different from the human brain, it is hard to imagine a mouse brain to which even a large number of human stem cells had been added ever functioning like a human brain.

Still other types of experiment might approach ethically problematic ground more closely in terms of the definition above. For example, in 2001, Ourednik et al. injected stem cells from a 15-week-old human fetus that had already specialized into brain stem cells, into the brain of 12 to 13 week-old primate fetuses (bonnet macaques).[10] When the simian fetuses were examined after 16-17 weeks, the human cells had spread to large parts of the brain and developed into different types of brain cell. The researchers estimated that there were up to 100,000 or so cells of human origin per monkey brain. The situation here, then, is that there are a considerable number of human cells present in an identifying organ of a closely related species. However, the human cells still only made up a negligible proportion of the total number of billions of cells in the monkeys' brains.

Another type of chimaera experiment deserves mention, although such experiments were apparently conducted only as animal-animal trials. The results, however, indicate that such experiments conducted e.g. from animals to humans could potentially be problematic, ethically, as we understand the concept here.

These involve various experiments on mice, in which embryonic mouse stem cells from one mouse were transferred to another mouse blastocyst and subsequently spread to the germline. The mouse will then produce germ cells, that do not contain its own genome.[11] If the experiments were conducted with human embryonic stem cells inserted into animal fetuses, ultimately it could lead to the animal producing human germ cells, and becoming pregnant with human embryos if it mated with other animals that were also producing human germ cells. As far as is known, however, no examples have been seen of any spread occurring to the germline across animal species, nor hence between human

[10] Ourednik, V. et al. (2001).
[11] Hochepied, T. et al. (2004).

beings and other animals, which would indicate that getting the embryonic stem cells to contribute to germline formation across species boundaries is not that straightforward.

Research into the development and function of organs

Other experiments, too, which seem to have been conducted as animal-animal experiments only, might potentially fall within our demarcation of what is ethically problematic if conducted between animals and humans. These are experiments involving transplantation of parts of organs rather than individual cells.

A certain amount of chimaera research has been done in which cells or organs are moved between chickens and quails – research whose purpose is partly to investigate how the brain develops and functions. For example, experiments have been performed in which specific parts of the brain in quail embryos are transplanted into the brain of chicken embryos. The chickens that develop have chimaera brains, and they display quail-specific behavioural traits.[12] Other trials serve to investigate the interaction between the brain and the sex hormones during quails' fetal development and the importance of this interaction for later sex-specific behaviour. In 2003 Gahr described, among other things, experiments in which part of the brain from female quail embryos was transplanted to male quail embryos. The male quails with partly female brains that developed from these transplanted embryos did not display the sexual behaviour typical of male quails.[13] These trials illustrate how changes in identifying behaviour can be brought about by brain tissue transplantation.

Creation of disease models

The point of some chimaera research is to produce animals with maximally

[12] See e.g. Balaban, E. et al. (1988); Balaban, E. (1997) and Long, K.D. et al. (2001).

humanized organs, which can be used to study illnesses and try out new treatments. The more humanized the organs, the better suited they may be as models.

A number of experiments have been conducted, for example, on creating a mouse model that can be used for investigations into human liver disorders if the mouse is infected with the hepatitis B virus. In 2005, for example, Katoh et al. succeeded in giving 20 to 30 day-old, immune-defective[14] mice an up to 90% humanized liver by infusing liver cells isolated from children.[15]

Thymus (an important gland that is part of the immune system located behind the breastbone), liver, lymph nodes and spleen from human fetuses have also been transplanted into immune-defective mice, and in this way mice have developed with a ”humanized” immune system – or, in short: mice with a human immune system.[16] Such mice can be infected with HIV and thus provide important knowledge about the development of the HIV infection and the possibilities for fighting it.[17] It is yet another example of a comprehensive mixture of cells from humans and animals in which large parts of a whole animal organ system have been rendered human.

Irving Weissman and his research group from Stanford sought permission from the University’s ethics committee in 2003 to carry out two experiments designed to produce mice with human brains that could be used as disease models.[18] In one type of trial the research group wanted to implant human, neural stem cells into the brain of mice that had been manipulated so that the neurons of the cerebellum (the little brain) degenerate some weeks after birth, in order to see whether the transplanted cells could re-form the functions. That would then show

[13] Gahr, M. (2003).
[14] The fact that the mice are immune-defective means that, owing to the lack of an immune system, they cannot reject foreign tissue.
[15] Katoh, M. et al. (2005).
[16] McCune et al. (1988).
[17] Namikawa, R. et al. (1988).
[18] Scott, C.T. (2006).

that the infused cells were working. In the other type of experiment the research group wanted to do the same with mice that had been manipulated so that all their neurons die approximately one week before birth, so that the fetus dies. Weissman and colleagues applied for permission to infuse human neural stem cells into the mice as they lie in the womb, and if the experiment succeeds, the surviving mice would have brains comprised entirely of human cells. A panel of bioethicists and researchers at Stanford University have stated that they deem the experiments to be safe but the researchers should observe the mice closely to see whether they develop unusual brain structure or behaviour. As far as is known, however, the experiments have not yet been initiated.

Development of new therapies

Part of the basic research aims to develop treatments for illness and disease, so there is a continuous transition between the categories. Below, however, we shall be looking at experiments whose primary purpose is to re-establish normal functions in sick or disabled people. Eventually, some of the treatments might also be used to improve normal functions, but that will not be focused on here.

Some trials are occupied with transferring cells between animals and humans in order to see whether foreign cells can remedy disorders that are due to particular cells in the body disintegrating. For example, in 2001, Castaing et al. implanted embryonic pancreases from 6-9 week-old human fetuses under the fibrous capsule of the kidney in immune-defective mice with degraded, insulin-producing cells to investigate the scope for treating type-1 diabetes.[19] The pancreatic tissue grew in the mice, insulin-producing cells developed and these produced insulin, which was able to regulate the mice's blood sugar normally.

[19] Castaing, M. et al. (2001).

Even fully developed organs have been transferred between animals and humans for therapeutic purposes. For example, kidneys from a rabbit, pig, goat and chimpanzee have been transplanted to human beings on an experimental basis.[20] One patient who received a chimpanzee kidney survived for nine months.[21] Other examples are transplantation of a heart from a baboon to an infant (which subsequently survived for 20 days)[22] and liver transplants from baboons to humans. One patient survived with a baboon's liver for 70 days.[23] These experiments can be hazardous, because the problem with the risk of transferring disease virus from animals to humans has not yet been solved.

Other experiments address the transfer of cells to closely related species' more identifying organs. For example, Bjugstad et al. are researching into the possibilities of using stem cells to treat Parkinson's disease. In 2005 the research group transplanted neural, pluripotent stem cells from a 13-week-old human fetus to an area of the simian brain (in African green monkeys) in which the animals' own dopamine-producing neurons were already destroyed.[24] After 4 and 7 months there were measurements indicating that the implanted cells were functional and had partly taken over the destroyed dopamine-producing neurons' functions in the chimaeric monkey brains.

Experiments have also been performed to transplant cells that can develop into germ cells, from humans to animals[25]. Here the intention is purportedly to cause animals to produce human germ cells, because it may possibly be a relevant treatment for people whose infertility is due to not producing germ cells themselves. Again, however, the animal that produces human germ cells might ultimately be envisaged as being able to fall pregnant with human embryos if it did mate with other animals that also produce human germ cells. However, no examples appear to have been published of experiments in which an animal has

[20] Reemtsma et al. (1964).
[21] Ahn, C. et al. (2004).
[22] Bailey, L.L. et al. (1985) and Walpoth, B.H. et al. (1986).
[23] Starzl, T.E. et al. (1993) and Collins, B.H. (2003).
[24] Bjugstad, K.B. et al. (2005).

successfully been made to produce human germ cells in its own reproductive apparatus.

As an example of the production of human sperm cells in animals, it can be mentioned that in 2000 Reis et al. attempted to transplant cells capable of developing into sperm cells, from human testicles to the testicles on immune-defective mice. After five months, however, there was no sign of fully developed human sperm cells having evolved.[26] If the trial had succeeded, the murine testes could presumably have produced both human and murine sperm cells.

With regard to the production of human ova in animals, it can be mentioned that some trials involve transferring egg-cell-producing tissues or organs between humans and animals with a view to investigating the possibility of making human egg cells. In 2003 Aubard transplanted human ovaries to mice, placing these either in the fibrous capsule of the kidney or under the skin of the mouse. The human germ cells were separated from the mouse's own reproductive apparatus, therefore. Examples have been seen of some follicular development, but there are no examples of mature human egg cells developing that were capable of achieving fertilization in such chimaeric mice.[27]

Research into reproduction and propagation

Hybrid and chimaera experimentation with the aim of producing offspring is of no topical relevance today - not of creating crossbreeds between animals and humans at any rate. All the same, it needs to be discussed here, as such experiments—if they were to be undertaken—could potentially lead to very extensive crossbreeds between humans and animals. Theoretically, human-animal crossbreeds could come into being if human germ cells in a test tube were

[25] Reis, M.M. et al. (2000) and Aubard, Y. (2003).
[26] Reis, M.M. et al. (2000).
[27] Aubard, Y. (2003).

combined with germ cells from closely related animals such as chimpanzees; or assuming animal stem cells were added to human embryos on a major scale in the early phases of development – most extensively when fusing embryos from humans and animals.

This type of experiment has been performed by fusing embryos from different animal species. Thus, as mentioned in the introduction, Fehilly et al. made the famous embryonic chimaeras between goat and sheep in 1984. These chimaeras were produced by mixing cells from very early goat and sheep blastocysts at a time when these had only been developed to the 4 to 8-cell stage. The chimaera embryos were subsequently inserted into either sheep or goat wombs and developed into adult chimaera animals with both goat and sheep characteristics.[28]

Conclusion

Several examples have been mentioned above of experiments that are problematic in the sense we wish to focus on here. There is particular cause to be aware of some types of experiments that can potentially affect identifying organs.

This may be, for instance, the transfer of human embryonic stem cells or neural stem cells to the brain of early fetuses or born experimental animals (primates, in particular) or the transplantation of parts of brains between humans and animals (again, primates especially).

In addition, transplanting germ cell-producing tissues or embryonic stem cells to early embryos, which could affect the germline, might potentially lead to the production of human embryos in animals or animal embryos in humans.

Finally, the ethical implications of producing animal-human crossbreeds, e.g.

[28] Fehilly, C.B. et al. (1984).

created as hybrids by combining germ cells from humans and animals, or through embryonic fusion of animal and human blastocysts, should be discussed in greater detail.

It is important to investigate whether such experiments are sufficiently regulated in the legislation and, failing that, to adapt it to ensure that experiments that are ethically problematic in the sense outlined cannot be performed in future.

Chapter 3
Chimaeras and hybrids, viewed from a legal perspective

Stem cell research has opened up new avenues for the exploration of treating diseases in human beings. Part of this research uses admixtures of humans and animals in the form of chimaeras and hybrids. Part of the reason for including animals is that there are narrow constraints on the interventions that can be performed on human beings, who are protected to a large extent by both ethical and legal standards. Conversely, certain things can be tested on animals, which do not enjoy the same protection as human beings in the legislation.

As yet, stem cell research involving a mixture of humans and animals takes place primarily at cell level, i.e. by studying cells' development, though there are also trials on the production of live animals which are chimaeras or hybrids. As will become clear from the following, the legislation sets limits on the development of creatures representing extensive crossbreeds of humans and animals.

This chapter paves the way for a discussion of whether this research involving an admixture of humans and animals is currently regulated appropriately in Danish law.

Legislation on humans and animals

It is altogether key that the legislation deals specifically with either animals or human beings – not both, as has also been illustrated in Chapter 1 of this report. The protection generally afforded by the legislation depends to a great extent on whether it involves an animal or a person. In the case of animals, the Danish Act on the Prevention of Cruelty to Animals places restrictions on what animals can generally be subjected to. When it comes to human beings, there are a wide range of rules that protect peoples' physical and mental integrity.

Differences central to the judicial take on humans and animals in this context include the view that every person must be an end in his or her own right and must not be reduced to just being a means, whereas an animal can be a means e.g. to obtaining new knowledge for the benefit of mankind.

Article 2 of the convention on human rights and biomedicine[29] establishes that ”The interests and welfare of the human being shall prevail over the sole interest of society or science”.

The preamble to the Animal Experimentation Convention[30] enacts that ”Accepting nevertheless that man in his quest for knowledge, health and safety has a need to use animals where there is a reasonable expectation that the result will be to extend knowledge or be to the overall benefit of man or animal, just as he uses them for food, clothing and as beasts of burden”.

An animal may be put down after conducting an experiment without giving any further reasons, whereas a human being may not under any circumstances be killed.

Section 7 of the Danish Act on Animal Experiments stipulates an obligation to put down an animal experiencing severe pain, any other intense suffering or intense fear, if this state cannot be alleviated by anaesthetization.
Section 237 of the Danish Civil Penal Code establishes an unconditional ban on killing a person, regardless of the reasons. Euthanasia is not permitted.

Crossbreeds consisting of both animals and humans can be difficult to fit into this framework unless unequivocally definable as either human or animal.

[29] European Convention (of 4 April 1997) for the protection of human rights and dignity of the human being with regard to the application of biology and medicine. Denmark ratified the Convention in 1999. Inter alia the Convention contains provisions concerning human subjects’ participation in trials.
[30] European Convention (of 18 March 1986) for the protection of vertebrate animals used for experimental and other scientific purposes. The Convention is enshrined in Directive 86/609/EEC (the Animal Experiments Directive).

Legislation on research

The mixing of humans and animals takes place primarily at research level today. In a legal context, therefore, the rules governing research, above all, are relevant in evaluating the extent to which the legislation places restrictions on the formation and development of crossbreeds.

Experiments with human beings

In Denmark legislation has been in place since 1992 for research in which human beings and human material are involved.[31] The legislation is intended to ensure that research projects are conducted in a scientifically and ethically defensible manner, and that consideration for the trial subject's rights, safety and well-being takes precedence over scientific and social interests. The law stipulates requirements concerning prior permission from a scientific-ethical committee before any trial can be instituted, if the research project involves live-born human individuals, human germ cells intended for use in fertilization, human fertilized eggs, embryos and fetuses, tissues, cells and human genetic constituents, fetuses and suchlike, as well as deceased persons. Research on cell lines are generally excepted from the duty to notify a scientific-ethical committee if the cell lines in question originate from a cell or tissue harvesting experiment that has qualified for the necessary approval. This exception does not apply, however, to research projects that include stem cell lines from fertilized human eggs. Such experiments have to comply with specific research purposes (cf. Section 25, see next page), and must therefore always be reported to a scientific-ethical committee, which must ensure that the experiment is confined within the parameters of Section 25.

The overarching parameters for the scientific-ethical committees' assessment of the research projects presented are given in Part 4 of the Committees Act on the

[31] Danish Act on a Scientific-ethical Committee System and Handling of Biomedical Research Projects.

committee system's remit. It follows from Section 12 that the committee can only grant permission *if* the risks that may be associated with conducting the project are neither per se nor in terms of the project's foreseeable benefits, indefensible in scope, and *if* the anticipated gain in therapeutic and public health terms can justify the project, and *if* the project's scientific standard fulfils the requirement that the project must contribute to the development of valuable, new knowledge, and *if* there are sufficient grounds for carrying out the project, and the project's conclusions are warranted.

There are no special procedures or deliberation criteria in the Act applicable to research projects aiming to mix humans and animals.

Other rules, however, are of specific importance to experiments with admixtures of humans and animals. These rules are found in the Danish Act on Assisted Reproduction in connection with Medical Treatment, Diagnosis and Research etc., which regulates *human reproductive technology*. The Act, which dates from 1997, contains rules that restrict access to research into early human life as well as research bans in relation to manipulating human beings as a species. In Danish law this Act is the only legislation that relates to crossbreeding animals and humans. The Act is applied in concert with the general controls on research, as mentioned above.

Restriction on research into early human life

Even at the cellular level the Act establishes certain restrictions on experiments that mix humans and animals. Whether the research project endeavours to develop a living crossbreed or "merely" study the development of cells is not crucial in this context. Nor is it crucial that humans and animals are mixed. What *is* crucial, however, is whether the experiment involves human germ cells or fertilized human eggs.

Section 25. Biomedical experiments on fertilized human eggs and on germ cells intended for use for fertilization may only be undertaken in the following cases:

…….

3) If the purpose of experiments using fertilized eggs and stem cells from the same is to obtain new knowledge capable of improving the scope for treating disease in human beings.

The potential of embryonic stem cells, in particular, preoccupies researchers. Embryonic stem cells are different from an embryo in one crucial respect, as stem cells do not have the potential to develop into a complete born human being. However, the clause does state that the same restrictions apply to research on embryonic stem cells as on fertilized eggs, as the original experiment on a fertilized egg can only be approved if the stem cells extracted from the egg during the experiment serve the permitted purpose in later use.

Section 25 does not cover human somatic cells or animal eggs. Insertion and reprogramming (nuclear transplantation) of human cells into animal eggs is not covered directly by the wording of the provision, then. The question is, though, whether, despite this, the situation falls within the scope of the provision. The intent of Section 25 is to protect a human embryo. Since the DNA of the mitochondria (the animal part) will make up only a very small proportion of the gene stock, the embryo in this example has the potential to develop predominantly into a human being. The example must therefore be assumed to be covered by the framework laid out by Section 25[32].

The reverse situation is also conceivable—a human egg in which the cell nucleus has been removed and replaced with a cell nucleus from an animal by nuclear transplantation. In such a situation the research involves a human egg – and is

[32] This assumption is supported by the Bioethics Convention's (convention on human rights and biomedicine) supplementary protocol on cloning, which emphasizes that it is the genes of the nucleus that are worthy of protection, not the genes from the mitochondria.

thus embraced by the wording of Section 25. The question is, though, whether, despite this, the situation falls without the law. What we have here, arguably, is a case of substantive atypicality, i.e. the situation is covered by the wording of the provision but not by its intent[33]. The intent of Section 25 is to protect a human embryo, not an animal embryo. In opposition to this view, there is arguably an essential, separate interest in protecting the actual human egg from manipulation, irrespective of whether the entity developed from it will contain only a very small human part.

It follows from the above that an experiment incorporating human germ cells for fertilization purposes, or a fertilized human egg, by admixing humans and animals in this context only will be legal if *its purpose is to study stem cells in order to thereby obtain new knowledge capable of improving the scope for treating disease in human beings.*

One essential restriction, however, is that under Danish law it is only permitted for research purposes to use fertilized human eggs that have been left over from treatment for involuntary childlessness (infertility), since it is not allowed to create a human embryo as part of an experiment. Even if – as in the above example - nuclear transplantation is performed, and the egg is not fertilized in the traditional sense, therefore, this results in the formation of an embryo by means of a special technique, which has the potential to develop into an individual, thereby covering it under the ban. Reprogramming human cells in an animal egg will presumably not be permitted, then, as this embryo will be human for the major part, cf. above discussion.

In this respect the Danish parliament also has certain obligations in terms of international law pursuant to its ratification in 1999 of the Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the

[33] Translator's note. Although this is self-explanatory in part from the context, the actual concept appears to be integral to Scandinavian law and has no direct English equivalent. It approximates to the canon of construction called the

Application of Biology and Medicine, which includes a ban on ”the creation of human embryos for research purposes”. One may well ask whether a crossbreed formed by means of nuclear transplantation (human cell in an animal egg) is ”human” in the sense of the convention. The supplementary protocol to the Bioethics Convention on Cloning highlights the fact that it is the genes of the nucleus that are worthy of protection, not the genes from the mitochondria. Since the crossbreed in this example is predominantly a human being (more than 99%) with only a hint of animal in it, it can presumably be labelled ”human” in the sense of the convention. It is currently not permitted, therefore. In the notes to the protocol, it is established that the ban on cloning includes all forms of nuclear transplantation with a view to creating identical human individuals.

It also follows from the Act that fertilized eggs may only be kept alive outside a woman’s womb for a fortnight from the time of fertilization. Fertilized human eggs that have been genetically modified for the sake of research may not be implanted in a woman’s womb.

Restrictions on the use of human germ cells and fertilized human eggs for research have a lengthy track record. The 1987 Act on the Formation of a Council of Ethics and the Regulation of Certain Biomedical Experiments took, for the first time in Danish law, a position on research access to fertilized human eggs, initially in the form of a ban on research.

In 1992 that ban was transferred to the Act on a Scientific-ethical Committee System and Handling of Biomedical Research Projects. Access to research in this field was made possible on this occasion, in that it was subsequently permitted to undertake such experiments with fertilized human eggs and germ cells as were necessary to ensure the proper therapeutic quality of in vitro fertilization. The same applied to other treatments for infertility, where a woman’s eggs are fertilized outside the womb. This was justified in part by the fact that keeping up

”Golden Rule of Statutory Interpretation”, doing justice to a case where a strict, literal interpretation would cause an absurdity.

a research ban would involve consciously offering women in need of artificial fertilization a treatment inferior to what was actually possible, placing these women at a disadvantage to other patients in the health services. Research projects with any purpose other than improving the fertilization technique with a view to inducing a pregnancy were still not permitted.

Compared to the earlier provisions of the Committees Act, the transfer in 1997 to the Act on Assisted Reproduction etc. saw an extension to the possibility of using germ cells and fertilized human eggs for research. In 1997 the field of research was expanded so as also to apply to research in techniques capable of enhancing pre-implantation diagnostics, and in 2003 the way was opened for experiments to harvest stem cells from fertilized eggs, providing the purpose of the experiment is to obtain new knowledge capable of improving the scope for treating disease in human beings.

The rationale behind this development has thus changed from stipulating special protection of the fertilized egg within a general research framework to a framework whose primary purpose is to create children. To this can be added the change in ethical discourse that occurred with the advent of stem cell research. The discussion about the acceptable framework for research on fertilized eggs is now no longer just about the ethical status of the fertilized egg, but also about sick people's need for treatment[34].

The main purpose of the provisions is not to prevent the development of creatures which are admixtures of humans and animals, but instead to restrict the scope of research in which human cells, which represent the very earliest development of a complete born person, can be used. From this point on, a potentially living person is being formed, and regardless of one's views on the ethical status of the embryo, there is broad consensus that, from the moment of fertilization, a human embryo is entitled to ethical and legal protection in relation to use in research. The deliberation in the legislation between the interest in developing new

knowledge for the benefit of curing diseases and the interest in nurturing respect for early human life has now been formulated in such a way that there is the possibility of incorporating human embryos in research for the purpose of obtaining knowledge about human diseases. The rules hinge on the ethical assumptions that regard for the protection of the embryo *can* be weighed against other considerations, and that the scope for developing treatments for severe disorders *can* weigh more heavily than regard for the embryo. The embryo may not, however, be kept alive beyond 14 days from the time of fertilization, and may not be placed in a woman's womb in modified form.

Thus it is prohibited to create a human embryo for research purposes. It is permitted to carry out experiments with human germ cells intended for use in fertilization and on fertilized human eggs and embryonic stem cells if the purpose of the experiment is to obtain new knowledge capable of improving the scope for treating disease in human beings. In the latter case a scientific-ethical committee must grant prior permission for such. A fertilized egg may only be kept alive outside a woman's womb for 14 days from the time of fertilization. Fertilized human eggs genetically modified for the sake of research may not be implanted in a woman's womb.

Ban on the creation of animal-human crossbreeds like hybrids and chimaeras

In addition, the law has certain bans on experiments enabling human-like creatures to be produced by admixture with other species. The chief purpose of these provisions is to prevent it from becoming possible to develop human creatures mixed with animals.

Section 28. The following experiments may not be conducted:

[34] Regarding such deliberations, see: Hartlev, Mette (2007).

1) *Experiments whose purpose is to make possible the production of genetically identical human individuals.*
2) *Experiments whose purpose is to make possible the production of human individuals by fusing genetically different embryos or parts of embryos before they take in the womb.*
3) *Experiments whose purpose is to make possible the production of live human individuals who are crossbreeds with a gene stock incorporating elements from other species.*
4) *Experiments whose purpose is to make possible the development of a human individual in a foreign (non-human) womb*[35].

These bans can be traced back to 1987, when they were inserted into the first Danish Act on the Formation of a Council of Ethics and the Regulation of Certain Biomedical Experiments. In the notes to the draft bill, it states that the ban on these types of experiment relates to ethically ”clear” situations, i.e. those situations where experiments serve no diagnostic or therapeutic purpose, and at the same time would clearly exceed the limits of what is ethically acceptable, in as much as the individual or species boundaries might be cancelled out. In the report entitled ”The Price of Progress” from 1984[36] it is said of the weighing-up of different considerations that need to be taken when introducing new technology that ”… techniques like cloning human individuals, producing crossbreeds of humans and animals and suchlike are examples that the ethical considerations clearly outweigh all others. There is no consideration for particular individuals[37]; on the contrary: in the final analysis, if they did become possible, the techniques would be capable of cancelling out the actual concept of human individuality. They clash with the species in an ethical and biological sense.”

[35] This provision was interpolated in 1992 in connection with the transfer of the bans to the Act on a Scientific-ethical Committee System etc.
[36] Danish Ministry of the Interior’s Committee on Ethical Problems in connection with Egg Transplantation, Assisted Reproduction and Fetal Diagnostics. 1984. *Fremskridtets pris. Etiske problemer ved gensplejsning, ægtransplantation, kunstig befrugtning og fosterdiagnostik* [”The Price of Progress. Ethical Problems in connection with Genetic Engineering, Egg Transplantation, Assisted Reproduction and Fetal Diagnostics”].

Irrespective of the fact that these experimentation bans have been moved several times, legislatively, from the Danish Act on the Formation of a Council of Ethics (1987) to the Act on a Scientific-ethical Committee System (1992) and since 1997 to the Act on Assisted Reproduction – they are still applicable. Thus it is forbidden to start research projects whose *purpose is to form and develop born living entities like crossbreeds of humans and animals if these entities can be characterized as "human".*

The bans focus on producing a living born being. The technique and human parts used in this process are not crucial, and the provisions can therefore be applied irrespective of how reproductive techniques evolve. In another way, however, the provisions are delimited relatively narrowly in order to bear upon the protection of the person. The chimaeras formed by the addition of foreign cells at the embryo stage are supposedly the most comprehensive chimaeras, because transplanting cells before the animal is fully developed will give the transplanted cells the chance to develop, spread and differentiate very extensively. Since the chimaera will develop most at the beginning of its development, the legality will presumably depend on when in the development of the embryo the human stem cells are added. The earlier on the human cells are added, the greater the likelihood of human traits developing. If the chimaera cannot be labelled as human, there is no ban under the law. It should be noted here that embryonic stem cells have the potential to develop all forms of cell. They can develop into brain cells, and also into germ cells – and hence with the risk of fertilization and development of partially human embryos in animals (or pure human embryos, if both the mother and the father animal produce human germ cells). A vital question in this context may be, therefore, whether the animal's producing e.g. human germ cells makes the animal human?

The law thus reflects the sharp demarcation mentioned earlier between humans and animals. Crossbreeds are only covered by the ban in Section 28 if the

[37] It was not found, therefore, that there was any consideration to be taken of patients with certain disorders, as the formation of hybrids etc. was not considered to have any therapeutic purpose.

creature can be defined as a ”human” individual. The criteria by which this should be determined is a difficult question not discussed in the preparatory works to the law. So the legislation provides no more detailed directions about demarcating the ”human” – whether this is a qualitative or a quantitative evaluation, or a combination of the two. The decision might be envisaged being made on the basis of quantitative criteria, e.g. how great a percentage of the creature is human or animal, respectively. Presumably, though, it will be very difficult to mark out limits concerning what implanted human cells can develop into, just as it will be difficult to delimit the human from the animal. The decision may possibly have to be made in accordance with qualitative criteria, e.g. behaviour, appearance or similar. However, it must be assumed that the lack of knowledge about normal non-humans' (e.g. primates') abilities may make it hard to measure whether the animal changes, and as shown by this report, there is no philosophical consensus on the moral importance of changes in animals' cognitive and emotional capacity. As such, the law draws a distinct borderline between the prohibited and the permitted, but this crucial and important boundary has been set using a concept that is in no way clear-cut.

Thus it is prohibited to perform experiments whose purpose is to make possible the production of genetically identical human individuals (clones), just as it is forbidden to perform experiments whose purpose is to enable human individuals to be produced like mosaics by fusing genetically different embryos or parts of embryos. Experiments whose purpose is to enable living human individuals that are crossbreeds to be produced, with a gene stock incorporating elements from other species, are also forbidden, as well as experiments whose purpose is to enable a human individual to be developed in an extraspecific womb. A scientific-ethical committee cannot permit such experiments.

Experiments with animals

There are also rules for animal experiments. These rules need to be seen in the light of an acceptance to use animals in experiments, where deemed to be of essential benefit and to yield important knowledge within the exploration of disease or the development of methods for curing disease. The rules focus on animal welfare and are intended to protect experimental animals from unnecessary pain and suffering.

Examples of animal experiments with chimaerization can be research that adds stem cells, body cells or whole organs from a human being to a (born) animal. Assuming the cells/the organ is/are assimilated, the creature is a chimaera. The intention in this context is either to create a disease model or to create a live animal with human organs or cells that are not rejected when transplanted to a human, e.g. a monkey with brain cells from a human, with a view to treating e.g. Parkinson's and Alzheimer's. There is no ban on chimaerization of a born animal by transferring human adult stem cells, body cells or transplanting entire or part organs. With regard to the use of human embryonic stem cells, there is no ban, as outlined above, if the purpose falls within the framework of Section 25, item 3. Here, too, there can be a risk of the embryonic stem cells developing into germ cells – or of human cells or organs, e.g. human ovaries, developing far enough to produce human germ cells in animals.

Use of vertebrates for experiments that can only be assumed to involve pain, suffering, fear or permanent injury to the animals as well as experiments including cloning and genetic modification (of the germ cells) of vertebrates may only take place with the permission of the Danish Animal Experiments Inspectorate. As construed by the law, the pain threshold—and hence the application of the law—"accrues" even when the animal is injected (the syringe criterion). For experimental purposes, animals (with the permission of the Animal Experiments Inspectorate) can be subjected to suffering that exceeds what animals may otherwise be subjected to under the Danish Act on the Prevention of Cruelty to Animals. An "upper limit" for the involvement of vertebrates in

research, however, is that the animal may not experience severe pain, any other intense suffering or intense fear.
Given that human factors are also involved in such an experiment, both a scientific-ethical committee and the Animal Experiments Inspectorate have to grant permission before the project can be set in train.

Experiments on animals in the fetal stage are not covered by the permission requirement if the experiment does not entail the animal being born. The Act on Animal Experiments and the Act on the Prevention of Cruelty to Animals protect living born animals only. There is no absolute fixed time limit for keeping an animal fetus alive outside of the womb. If the animal fetus is implanted and further developed in the womb of a living animal, the experiment is covered by the permission requirement.

Conclusion

Fundamentally, the legislation is currently based on a demarcation between animals and human beings. The admixture of animal and human can be difficult to fit into this framework.

Creation and use of germ cells and fertilized eggs

Early human life

The legislation establishes restrictions on the creation and use of early human life in research. To a certain degree these rules restrict the formation and further development of hybrids and chimaeras, stipulating not only a ban on creating a human embryo for research purposes alone but also a requirement in terms of the purpose of the experiment (to study stem cells in order to thereby obtain new knowledge capable of improving the scope for treating disease in humans). The backdrop to these rules is a wish to nurture respect for human life from the very point of fertilization. Embryos generally do not enjoy the same status in the

legislation as born human beings, but the potential of the fertilized egg to develop into a born person affords it special status and protection in the legislation, which other forms of human cells and tissues do not have. To govern the use of human embryonic stem cells, the legislation fixes the same constraints as for fertilized human eggs, as the embryonic stem cells are extracted from a fertilized egg, which then perishes in the process. A human embryo may only be kept alive outside a woman's womb for a fortnight. The embryo may not be implanted in the woman's womb in modified form.

Early animal life

There are no rules restricting the use of early animal life.

Thus there is no ban on research projects whose intention is to test the potential of human embryonic stem cells in unborn animals when the purpose of the project is to obtain new knowledge capable of improving the scope for treating disease in humans. A scientific-ethical committee must grant permission before the experiment can be set in train.

Creation of born entities as a mixture of human and animal

Ultimately, research into the formation of crossbreeds is restricted nowadays by the current ban in force on creating born live human creatures mixed with animal. The backdrop to these rules is to protect humanity as a species from any attempts to test and extend species boundaries. The rules further have the clear function of preventing the ethical and legal problems that can arise if a live being, as a mixture of human and animal, achieves human status under the legislation. The rules do have their shortcomings, however.

Creation of a human person with animal mixed in

Firstly, they leave it largely to the user himself to ponder when a creature can be regarded as "human". This can be illustrated by some of the types of research

into chimaerization between humans and animals highlighted in this report as being ethically problematic, in as far as they can potentially create doubt whether the creature is animal or human[38]:

1) It may be, say, an experiment in which vast amounts of human embryonic stem cells or neural stem cells are transferred to the brain of early animal fetuses with a view to creating an animal with a partly humanized brain. A question crucial to whether the experiment falls under the ban will be whether the presence of human brain cells in the animal makes it human.

2) Another example may be an experiment involving transplantation of germ cell-producing human tissues, or of human embryonic stem cells to early animal embryos, which could affect the germline. This could lead to the production of human embryos in animals. A crucial question in this context will be whether the animal's producing human germ cells makes the animal human.

3) A third example of experimentation may be the production of animal-human mixtures created as hybrids by combining germ cells from humans and animals, or by embryo fusion of animal and human blastocysts. This creature will undoubtedly be characterizable as human, and is thus banned. It should be added here that, according to the legislation, this form of admixture will be banned even at the formation stage.

Thus it is prohibited to develop a human being which is partly animal. A committee cannot grant permission for this.

Creation of an animal with human mixed in

Secondly, these rules relate solely to the formation of creatures that are predominantly human. They do not, in other words, relate to lesser degrees of humanization. Animal legislation imposes limits on the creation of such

[38] See Chapter 2.

creatures. According to this, it is allowed to involve animals in experiments if the purpose of the experiment is to develop knowledge about treatment. The animal must not experience severe pain, other intense suffering or intense fear, however.

There is no ban on creating an animal that is partly humanized with a view to obtaining new knowledge about therapeutic possibilities. Both a scientific-ethical committee and the Animal Experiments Inspectorate must give permission for the experiment. Permission cannot be granted if the animal is going to be subjected to severe pain, or experience other intense suffering or intense fear.

Species modification of creatures already born

The bans mentioned relate purely to the *development* of a human-nonhuman mixtures. They do not relate to the humanization of an already born animal – or to the transfer of animal tissues to an already born human being.

Humanization of an animal

Nor does the animal legislation take up an explicit position on attempts to modify an already born animal in the human direction. Chimaerization on born animals is limited, however (to some degree), by the rules protecting live experimental animals. The application of the rules to some of the types of research in chimaerization between humans and animals, highlighted in this report as being ethically problematic, can be illustrated by means of the following examples:

1) It may be an experiment in which neural stem cells are transferred to the brain of experimental animals (especially primates); or the transplantation of parts of brains – or whole brains – between humans and animals (again, primates in particular).

2) It may also be an experiment involving the transplantation of germ cell-producing human tissues, or of human embryonic stem cells to animals, which will influence the germline. This might potentially lead to the production of human embryos in animals.

There is no ban in the legislation on adding human embryonic stem cells, body cells or whole organs to an animal with a view to creating an animal model with maximally humanized cells or organs as long as the purpose of the experiment is to obtain new knowledge capable of improving the scope for treating disease in humans—regardless of whether the animal thus becomes human. The experiment requires the prior permission of both a scientific-ethical committee and the Animal Experiments Inspectorate. Permission cannot be granted if the animal is going to be subjected to severe pain, or experience other intense suffering or intense fear.

Transfer of animal tissues to a born human

Since such forms of experiment involve a live human being, the experiment is shrouded by a wide range of rules that protect the individual person's physical and mental integrity. Live experimental animals are protected by the animal legislation, as mentioned above.

There is no ban on attempts to transplant cells or organs from animals to human beings. Both a scientific-ethical committee and the Animal Experiments Inspectorate must grant permission for experiments.

For all types of experiments, it is true to say that the experiment has to be ranked, legislatively, because the protection afforded by the legislation depends largely whether it involves an animal or a person. Where a creature consists of elements of both animal and human, this *combination can be difficult to fit into the current legislative framework* for research, as it presupposes a sharp division into experiments on humans and experiments on animals.

An extreme limit on permissible research projects according to the legislation is that animals may not be created in such a way as to lend prominence to the human element. Developments in research have now generated a need to partly *define the human* and partly *re-evaluate the legislation in the light of the technical-scientific possibilities of modifying the natural creation process*.

Legislation in the field takes the form of laying down certain prohibitions and restrictions, combined with a general requirement for permission from a body appointed for the purpose before experiments can be set in train. Some research projects require permission from two bodies, one evaluating the animal, the other the human aspect. These *permission systems too are based on a sharp division of humans and animals.*

Chapter 4
Are there ethical problems with hybrid/chimaera research?

In Chapter 1 we attempted a demarcation of the forms of research in human-animal chimaeras or hybrids that must be regarded as crossing the dividing line between humans and animals, in a non-trivial sense. From Chapter 2 it emerged that parts of the chimaera research currently in progress could potentially result in creatures that were modified in some significant way.

The immediate reaction on the part of many people on hearing about human-animal crossbreeds is one of disgust and loathing. These gut reactions are generally good reason to stop and examine why a phenomenon such as mixing human beings with other species provokes such emotions or intuitions that something is amiss. For some, the loathing in itself will be sufficient reason to reject chimaera research. This was true of Leon Kass, for example, who states that:

> *"Indeed, in this age (..) in which our given human nature no longer commands respect, (...) repugnance may be the only voice left that speaks up to defend the central core of our humanity".*[39]

And yet most people would surely concede that emotions and intuitions have their limitations as reasoning, as long as they merely take the character of more or less unarticulated feelings. Furthermore, such notions are culturally malleable and historically changeable; for example, most people in Denmark 100 years ago would presumably have been able to agree that homosexuality was unnatural and repulsive and should be banned, whereas today it is commonly accepted, and

[39] Kass, Leon. (1997).

the state sanctions partnerships between people of the same sex.

Kass also concedes that violent revulsion is not an argument, for the above mentioned reasons, but he does maintain that:

> *"In crucial cases, however, repugnance is the emotional expression of deep wisdom, beyond reason's power fully to articulate it."*[40]

The question then becomes how we can separate those situations in which repugnance is possibly an expression of deep wisdom from other situations in which it proves to be a historically or culturally conditioned response. Normally, even those who argue in favour of emotions and intuitions having to be assigned considerable weight in ethical deliberation think it necessary to draw up criteria for when that repugnance has to be attributed importance.

One may consider the importance of inherited mechanisms for the protection of the species—that is to say, establishment of species barriers, which can be chemical (incompatibility), physical or behavioural in nature. Species barriers can be described in natural-science terms as the product of evolution. Hence, it is not inconceivable that such revulsion for the weird can have a biological rationale. That is hard to answer, however; for both that which resembles the human yet is not so, and that which is remote from anything human, will be capable of arousing revulsion. There is no certainty that people will entertain revulsion for fabulous chimaeras at first sight, but it is surely crucial whether the fabulous being has human facial features. For example, most people will react with greater repugnance towards a minotaur, which has a bull's head on a human body, than towards a centaur, which has a human head on a horse's body.

It is only fair, then, to look for reasons for the intuitive revulsion which crossbreeds between humans and animals evoke in some people. We will put forward six types of arguments claiming that the production of human-animal

chimaeras would give rise to ethical problems. The arguments are not mutually exclusive; one can certainly endorse a number of the reasons simultaneously, therefore. Conversely, one can also endorse one or more of the reasons without thereby adopting a final stance on the issue of whether the production of human-animal chimaeras is ethically wrong. There may be weighty opposing considerations, e.g. in terms of the usefulness of the relevant research, which means that from an overall point of view the form of research concerned is deemed ethically acceptable.

Creating chimaeras is wrong if it violates humans' or animals' God-given dignity

Customarily, we assume that animals of all species have dignity, and that mankind has very special dignity. As will become clear below, some people will justify mankind's special status and dignity with the very special—particularly cognitive—abilities and qualities that human beings possess. Others will find this justification inadequate; it is clear, after all, that we also regard e.g. deeply retarded people as having dignity entirely on a par with all other human beings – irrespective of their mental disabilities. If human dignity is to be founded in something, it cannot, on the basis of that consideration, just be a question of particular qualities or abilities. From the perspective of such a philosophy, the dignity of both humans and animals, e.g. in accordance with a Christian understanding of life, would be regarded as something gifted by God through the creation of the species and the coming-into-existence of every single person or animal. This *creation-oriented view* entails God having placed a particular order in the world, according to which man, as created in God's image, has a special status and responsibility for stewarding nature out of respect for the Creator. The key principle here is that human dignity and ethical status cannot be derived from anything empirically ascertainable. Mankind has been granted his special

[40] Ibid.

dignity. Primarily, it is not a biological phenomenon, then, but must be viewed in tandem with mankind being seen not only as something material and biological but, to use Grundtvig's words, as being "an experiment of dust and spirit".

One aspect of the creation-oriented view is that nature encapsulates a deep wisdom, inter alia about the relationship between the species. The view also entails all created things having dignity and us as human beings having to exercise our stewardship of nature in the light of that, out of deference to the Creator.

The creation-oriented view need not be interpreted so strictly as to eliminate absolutely any question of modifying the human body if there are weighty reasons for doing so, for example with a view to combating disease. But in embracing the view, it would generally reflect a lack of respect for the Creation (and hence for the Creator) if such extensive chimaeras were to be produced that they led to radically altered species – perhaps even altogether new species.

From this point of view there is no determining precisely where to draw the line between human and non-human. But at any rate it does follow from the view that it would be unethical if a human life were to be made into a non-human life through chimaerization.

The creation-oriented point of view invites a great degree of caution. Based on this view, very good reasons are needed, firstly, for wanting to introduce animal cells into a human being. In general, it should only be done on the grounds of effecting a cure for some severe disorder that cannot be cured in any other way. Secondly, the requirement must be that there is a high degree of certainty that the germ cells will not be affected by the intervention so as to effect changes to any future generations.

Where human cells in animals are concerned, the basic premiss must be consideration for the dignity of both human beings and animals. From a creation-

oriented point of view, therefore, very good reasons are also called for if such an intervention is to be accepted. Moreover, here again, one requirement must be that there is a high degree of certainty that the germ cells will not be affected by the intervention.

Producing chimaeras is a violation of the natural order

The point of view taken as a basis for a number of the other considerations presented, namely that the ethical problems associated with producing chimaeras are best identified on the basis of the ”ethical status” to which the creatures or species involved can lay claim, is far from absolute or universal. For instance, the Danish theologian and philosopher K.E. Løgstrup asserts that one is committing a civilizing error if one regards the universe as blind and deaf and insensitive. The universe contains a life-giving and order-forming power that constantly feeds through into living nature, including human life. The opposite of this, according to Løgstrup, is to regard ’nature’ purely and simply as a surround to – and a raw material for – the development of human ingenuity:

> *”Everything natural science tells us about nature and the universe, we are prone to take as information about what does not regard us in any way other than the world around us. Indeed, in what other way should it concern us then? As our originator! All the more since it is not just in the past during a long development process that human existence arose from nature and the universe, but it is still doing so, repeatedly and in the most tangible fashion. With respiration and metabolism we are embodied in the cycle of nature, with our senses we are embodied in the universe.”*[41]

Based on an alternative and broader concept of experience, Løgstrup defends the notion of the natural order as value-bearing. He acknowledges that the viewpoint

[41] Løgstrup, K.E. (1984): 11.

is up against powerful forces in the dominant school of thought, but nevertheless recommends *"the possibly impossible, to swivel our attitude 180º around its own axis and come to the realization that the universe is not our surround but our originator."*[42]

The view invites a show-down with anthropocentrism and the point of view cognate with anthropocentrism, which also allows the higher-ranking animals membership of the privileged gentlemen's club by virtue of the fact that they share with man the ability to feel and suffer.

The alternative to anthropocentrism calls for openness towards the life-giving and order-forming power of the universe, for deference to the created and a humble cautiousness in man's treatment of natural phenomena. As of the beginning of the 20th century, the adverse consequential effects of rolling out anthropocentrism in practice were minor enough to be overlooked, but during the past 50 years, in which technologies have become ever more potent, the consequences seem to have become more and more unmanageable according to the alternative point of view. The more violent the interventions man is capable of making in what has hitherto been regarded as "the natural order", the greater the civilizing hubris seems to become—despite the fact that the accelerating growth of such forces, according to this highly alternative philosophy, ought to call for greater caution.

According to adherents of respect for the natural order, the various chimaera experiments of the biological sciences are characterised by an anthropocentric way of thinking. Practitioners of modern biology allegedly fail to acknowledge that the natural order contains a virtually inconceivable wisdom that a few generations of gene researchers and biotechnologists cannot grasp at first sight, let alone *disregard.* So when, for instance, researchers produce chimaera chickens with "quail-specific behavioural traits" or mice with the ability to

[42] Løgstrup, K.E. (1982): 9.

produce human germ cells[43], viewed from this point of view in question this is a case of anthropocentric hubris.

The aim of that kind of experiment is nearly always noble, but according to trend-setting adherents of the idea of respect for nature, it is seldom the goal that changes the world as much as the side-effects of pursuing that goal. K.E. Løgstrup actually speaks of ”the world-transforming power of side-effects”.[44] In our zeal to evaluate and measure the individual, isolated phenomena in our scientific experiments – including evaluating and measuring them ethically— according to Løgstrup, we easily overlook the societal entity within which such side-effects make themselves felt.

The line of thought outlined here—that the production of chimaeras is a violation of the natural order whose knock-on effects on both culture and nature are impossible for us to grasp—does not automatically lead to a ban on any research project that involves the manufacture of chimaera cells. But it does lead to greater cautiousness in our treatment of that kind of research.

The view does not imply that nature represents a constancy which mankind ought to give a wide berth. E.g., Løgstrup feels that mankind has been allowed into nature and as such, therefore, mankind has always intervened in the course of nature—in many instances with positive effects as a result. Few, for example, will think it wrong to eradicate the smallpox virus, although it constitutes an interference with nature.

There may therefore be grounds for asking for reasons to be given why the production of crossbreeds should be any greater a violation of the natural order than, say, penicillin treatments. Is it due to the fact that some scientific interventions seem more ”radically unnatural” than others or, rather, to the long-term consequences appearing to be all too unfathomable.

[43] See the examples in Chapter 2.
[44] Løgstrup, K.E. (1982): 17-24.

Adherents of the idea of respect for nature will typically answer that no abstract reply can be given to such questions. When it comes to intervening in nature, what is acceptable and what is borderline has to come down to a case-by-case assessment.

Risk and scientific uncertainty

A different type of reasoning for human beings refraining from interfering radically in the natural order can be that it is simply too risky in some cases, because human beings lack sufficient knowledge about the composition of nature to be able to take in the long-term consequences of the intervention. It is hubris to believe that we can oversee the consequences. This is a problem particularly in the case of interventions that not only concern the individual being treated but perhaps concern the germ cells and will therefore be transferrable to future generations.

The researchers working with such technologies are often optimistic and may therefore overlook potential hazards, but even when they are open to something possibly going awry, it is impossible in some cases for the researchers to predict what can go wrong in this type of research. There is no need, therefore, to be suspicious of the researchers' foresight in order to acknowledge that making alterations to future humans and animals involves uncertainty and risk. By the very nature of things, then, we have no experience of what the long-term effects of such alterations will be, so the risk of unforeseen side-effects is ever-present. We have seen this, for example, in certain segments of animal biotechnology, where interventions—reproductive cloning, for example—have resulted in problems for the animals concerned and their offspring.

In addition, the transfer of cells or organs from animals to human beings can be risky because it involves a danger of transferring diseases together with the cells.

This is a problem with xenotransplantation, where one barrier to the use of animal organs as a substitute for defective organs in human beings is the fear of a virus from the animal being transferrable to the person on the receiving end of the organ. The recipient may subsequently infect other people and perhaps even start epidemics of incurable diseases. Today we know that the great Spanish flu epidemic, which killed 100 million people at the beginning of the 20th century, was caused by a porcine virus being transferred to humans, and at any rate some types of HIV constitute other examples of viruses that, in mutated form, are thought to transfer from animals to humans.

For some these uncertainties and possible hazards will, per se, be sufficient to ban chimaera research. Others will consider the most important ethical point here to be the magnitude of the benefits that research needs to generate in the form of treatments for severe diseases—or identification of essential knowledge—in order to justify a particular risk. This is not a simple one to answer, and requires thorough assessments of each individual research project.

Creating chimaeras is wrong if it violates the crossbreed's human dignity

One suggestion for a possible way of understanding human dignity in relation to the creation of crossbreed creatures is the Kantian understanding. Other takes on human dignity attach importance to aspects other than the cognitive ones, but here we wish to use Kant's understanding of human worth as a baseline, synonymous with the special status accorded to human beings because they are moral creatures that can set themselves goals.[45] Other competences, too, can reasonably be included, and Cynthia B. Cohen proposes this definition: "Human dignity is a multi-faceted notion that is characterized by a family of unique and valuable capacities generally found in human beings. No one of these capacities is

[45] Kant, Immanuel (1785).

definitive of human dignity, but taken together, they set out a paradigm case of what it is to have human dignity"[46]. She understands human dignity to be associated with our ability to reason rationally, act morally or independently, feel empathy, have a social life etc.

This accords with the other type of reasoning normally given for ascribing human beings different ethical status to animals. Many will justify the special status of humans in concrete, cognitive qualities, and here most people point to different combinations of higher consciousness functions and social characteristics: the ability to relate to oneself and other humans, the ability for self-determination, the ability to act morally, the ability to see one's own existence as valuable, the ability for religious views, the ability to relate to one's own future, and so on.

Some people feel that a logical consequence of the notion of assigning ethical status on the basis of cognitive qualities is that most animals should be attributed ethical rights. They should, if they possess particular individual characteristics such as, say, the ability to feel joy or pain, to have desires, memory and a sense of the future. Very few, however, will think that animals must have the same high moral status as human beings, because animals' abilities and hence desires for a good life are different to humans'.

Working from this basis, it would be a violation of human dignity to consciously create a crossbreed in which all or some of these characteristics have been degraded or removed. Since many of the interventions will presumably be performed on fertilized eggs, the debate involves taking a stance on whether to consider these as human beings with human dignity, which can be violated. Some will feel this way, whereas others will find, rather, that the embryos' potential to develop the characteristics we associate with human dignity does not a priori give them human dignity capable of violation. Nonetheless, for adherents of the latter view too, conducting experiments that degrade or remove these characteristics from future human beings may violate human dignity. From a

[46] Cohen, Cynthia B. 2003.

Kantian perspective, the production of such creatures can be regarded as a violation of mankind's dignity as such, because in this way the researchers are using a potentially human individual solely as a means to promote their own ends, and in the process they are taking away the characteristics that could have imparted human dignity.

Conversely, it is possible to envisage many chimaera experiments that will not violate human dignity, because they do not affect the characteristics mentioned. But in theory, for example, experiments involving the transfer of pluripotent or neural stem cells or brain tissues to fertilized eggs or fetuses could affect the social characteristics in the recipient. Here, however, some will feel that there may be a need to distinguish between different hypothetical scenarios. For them it will be relevant to ask whether it makes any difference in relation to the potential violation of dignity whether the 'product' is:

A. A basically human creature being "upgraded"; this might be, for example (and entirely hypothetically), by having parts of an animal brain added and thus having the sensory apparatus expanded.
B. A basically human creature being "degraded"; e.g. by having parts of an animal brain added and thus having essential cognitive abilities destroyed.
C. A basically animal creature being "upgraded", e.g. by having parts of a human brain added.

Whether we are talking about one type of crossbreed creature or another may very well make some difference to the possibility of violating dignity:

The first two examples probably entail interventions on human embryos or fetuses. In this context some will argue that even undertaking such experiments violates human dignity. But in the sense in which human dignity is understood here, it is hard to see that the first type of change is supposed to constitute a violation at the level of the individual. Any such creature thus enhanced would probably still be considered a person in as far as it did not suffer any impairment

of its cognitive characteristics, which make it a person with full human dignity.

Of course, it can be difficult to envisage the consequences that such an ”enhanced” person would experience by, say, being given a much more delicate sensory apparatus than other human beings. Problems other than violation of dignity might arise in this narrow sense. For instance, such a crossbreed creature could have a debased life because it would have a radically different view of life to the people around it. It would also be a form of violation of dignity to create a creature with impaired quality of life, but in a different sense to the one we are talking about here.

In the other imaginary situation, a researcher, as mentioned above, produces a mainly human creature, which has had animal cells or organs added that have diminished its cognitive capacities. In the process, then, the researchers have consciously violated this human being’s dignity. Karpowicz et al. Put it thus:

> *”The torturer or the enslaver of human beings denies them the option of exercising the capacities associated with human dignity. The creator of the human-nonhuman chimaera would do even worse—he or she knowingly would diminish or eliminate the the very capacities associated with human dignity.”*[47]

As mentioned earlier, the violation of dignity in this case would perhaps be against mankind as such rather than against the individual, who is created with fewer cognitive abilities than it otherwise would have had.

However, when we come to the third example, by contrast, where a creature that is basically an animal has its cognitive characteristics enhanced, it is slightly more difficult to gauge in relation to this definition of violation of dignity.

Assuming that the moral status (or dignity) of the creature is enhanced when

given more cognitive characteristics, the addition of human brain tissue would increase the experimental creature's moral status. That in itself need not be morally problematic, of course, but it might become so if the creature produced were not treated in a way that lived up to the moral status it had acquired.

Probably, the enhanced creature would still be regarded as an animal, and would thus not be protected in terms of its enhanced moral status. For the purpose of medical and other research practice, human beings are assumed to have a moral status that prevents them from being subjected to experiments in which they may suffer harm or molestation. Conversely, many good research causes can justify disregarding even the most fundamental interests in animals.

The problem would therefore consist of us insisting, in practice, on classifying humans and animals in biological terms and continuing to treat the crossbreed as an animal. If, instead, we introduced a moral classification, in which an individual that has a sufficient number of cognitive characteristics is given status and a claim to protection as a person, there would be no problem for the individual. There again, a number of other problems would arise, and not just for the research projects in hand. Such problems would concern the whole way in which we have organized and marshalled our society.

Creating human-animal crossbreeds will violate the taboo against mixing species

A fifth type of proposal as to why it is ethically wrong to overstep the species barrier between humans and animals is that such overstepping is capable of threatening certain central social values.

From a rationalist point of view, which after all does not exhaust the taboo

[47] Karpowicz, P. et al. (2005).

concept[48], the ban on overstepping the species boundaries can be seen as a social taboo based on a perception that we are protecting essential social values by ring-fencing them with taboos. Viewed from this angle, it may be claimed that the notion of humans and animals being two entirely different categories with entirely different needs for protection is such an important social mainstay that it must be protected by a social taboo. In that case it may be obvious to look at what sort of social practices this taboo is intended to protect. Whether, in other words, it is an outdated taboo, which is ripe for abandonment, or whether the taboo denotes that overstepping the species barrier between humans and animals would actually have major negative consequences.

These negative consequences might be, for example, that abandoning the notion that humans and animals are two qualitatively different categories that have to be assigned different moral status would create moral disorder. Species boundaries may be thought to have an essential, socially conservative function, precisely because they allow us to look at animals as qualitatively different individuals to human beings – individuals that we can use for research, eating and keeping in captivity.

According to the anthropologist Mary Douglas[49] all societies have social taboos, which serve to preserve key social values by tabooizing practices that would be detrimental to the preservation of those values.[50] From this social angle, however, taboos are not universal—different things are taboo in different cultures. In addition, they are historically changeable, i.e. a taboo may have had its day and be dropped, as for example with the taboo against marriage between people of different colour, which has become outdated and been abandoned.

[48] Inter alia, the perceived view of taboos described as historically relative and basically man-made phenomena is not shared by all debaters of the taboo concept. Rational language has translated the concept of taboo using the word *forbidden*, but it simply means that it is dangerous—a dangerous area which needs thinking about twice before approaching or being prepared to approach. On the difference between rational language and mystical language, see Sløk, J. (1999), 209 and 295.
[49] Douglas, Mary (1966). (Here, from Morriss, Peter (1997).)

Social taboos are often rooted in some basic classification systems that we use to define the world and bring order to its chaos. The classifications are important to us, and we react to them being ignored with fear and hostility, because dismantling them causes us to lose our grip on the world. For instance, the taboo against killing people has an important social function, and abandoning it might very well lead to altogether chaotic states. In the same way, the family is (still) a mainstay of social structure in our society, and for that very reason it is important for us to be able to keep the different relations between family members apart. That might be one of the reasons why the notion of a surrogate mother being able to give birth to a child to which her daughter is the biological mother evokes such violent reactions. One cannot be both mother and grandmother to the same child. That throws family relations into disarray and is one of the reasons for outlawing such arrangements.

Human-animal crossbreeds can be viewed from the same angle, being classifiable neither as humans nor animals. The mere existence of such creatures may be felt to threaten our classification systems. In a way they obliterate the species barrier between us and the animals and thus threaten our social identity and our unique status as human beings.

Common to taboos is their symbolic nature, but in our culture it is normally not enough to lend them legitimacy. Hence, there is often felt to be a need to investigate taboos scientifically. For example, it is a widespread view, and one which tallies with most people's experience, that species boundaries are biologically well defined. In actual fact, however, it has proved very difficult to determine universally valid definitions for species. According to some sources, there are currently up to 26 such definitions in the biological literature, none of them universally tenable.[51] Moreover, a lot of recent research indicates that the differences between human beings' and animals' abilities and skills are smaller

[50] Taboos, however, can also be seen in the light of a different rationale; for example, this might be concern about overstepping the limits of the unnatural.
[51] Robert, J.S. and F. Baylis (2003).

than had previously been assumed.[52]

In the case of crossbreeds, the taboo's universal validity and applicability can always be questioned, at least where our world picture is concerned. The ancient Egyptians, for example, depicted some of their most venerated gods with animal heads or bodies, and the American Indians also had sacred figures that combine humans and animals. Our literature – and particularly, perhaps, children's books—also feature examples of crossbreeds between animals and humans occurring as something fairy-tale-like and innocuous.

Taken to the extreme, such lines of reasoning can lead for some to the conclusion that contemporary species boundaries hinge on a social taboo, one to which we adhere primarily for fear of having our fixed divisions of the world upset. It may be claimed that if this division of the species does actually hinge on a taboo, it is time to abandon it, as we have previously abandoned the taboos against, say, blood transfusions, organ donation, marriage between black and white people, and homosexuality. Like them, the taboo against species crossbreeds has its roots in a particular historical and social context, and as those contexts change, the taboo will lose its meaning too. Many will claim that the taboo against mixing animals and humans is already undergoing disintegration, for example with the acceptance of implanting pig's heart valves into humans.

Others, however, will argue that although we need to acknowledge that species boundaries may hinge on a taboo, we have no choice but to maintain it because the social consequences of abandoning it will be too great. It is pointed out that the division between humans and animals – regardless of how uncertain this can be said to be – is an example of a boundary that actually performs an important function.

[52] Morriss, Peter (1997).

Crossbreeds will cause serious moral confusion

Robert and Baylis put a slant like this on the discussion.[53] They acknowledge that the majority of arguments against the crossing of species boundaries are based on unsubstantiated biological definitions of species as well as on fuzzy moral categories. But working from a variant of the moral taboo argument, they reach a different conclusion, as they fear that it would give rise to moral confusion both in our present relationship with animals and in our future relationship with partially human hybrids and chimaeras, if the border between humans and animals were definitively dismantled.

Their point is that, although we admit that some higher-ranking animals have many of the cognitive characteristics we associate with moral status, this insight has not assumed any major importance for the way we configure our lives in practice. For example, a majority in society accepts research on all types of animals if it is for a good cause. Research into human-animal hybrids and chimaeras will focus on the dubiousness of this practice if it leads to the creation of individuals that cannot be slotted into the biological division into species, because in as much as we would be unable to answer the question of what moral status to ascribe to individuals that are neither animals nor humans, it would focus on the fact that, in practice, we ascribe moral status as a function of an untenable biological boundary. But if we were to act on the basis of this admission, it would have unmanageable consequences for our way of self-organizing and our appreciation and understanding of our moral obligations towards animals, towards other human beings and towards such creatures.

It could thus be argued that the social and societal consequences of abandoning the notion that human beings have a different moral status – and hence other rights and entitlements to protection – than animals, *might* become far greater than the consequences of previous redefinitions of, say, the status of women or

[53] Robert, J.S. and F. Baylis (2003).

people of colour.

Assuming a more radical redefinition of humans' and animals' moral status, the consequences for research, for animal husbandry and for our eating habits, amongst other things, could be very far-reaching.

For if moral status is to be ascribed to individuals on the basis of their specific qualities rather than their affiliations to either the human or the animal grouping, a number of human individuals (newborns, severely mentally retarded and comatose people etc.) would presumably be unable to meet the requirements needed to be considered as persons. By the same token, a number of higher-ranking animals we currently regard as legitimate experimental subjects would presumably turn out to be entitled to protection they do not currently receive. How it would supposedly be feasible, in practice, to set out concrete criteria for ascribing moral status is a question in its own right. But what the practical consequences for e.g. research, animal husbandry and eating habits will be, is altogether unimaginable.

Can medical trials on animals continue if we abandon the notion that species affiliations have moral significance? What criteria should researchers then apply regarding which individuals they would be allowed to use for research, and according to what rules must informed consent be given? May the experiments be painful and risky? May the creature be euthanized if the experiment has an adverse outcome?

The gist of many objections to Robert and Baylis's position is that the confusion as to who is to be ascribed moral status is not new. Previously, groups like women and people of colour, for instance, were not part of the group accorded full moral status. But just as, historically, we have been able to change their status, without causing insurmountable moral confusion, we will also be able to accommodate these new types of creature. It is not plausible to claim that upgrading animals will have greater consequences than upgrading other groups,

such as slaves and women.

But even conceding that abandoning species boundaries will pose a serious threat to the social order, it is surely not a sound reason for maintaining a practice if we have to acknowledge that it rests on an untenable basis? If the untenable basis is that we do actually treat animals worse than they are entitled to, perhaps we ought to be changing our practice instead of trying to defend our privileges at the expense of the animals.

The members' positions

As mentioned at the start of this chapter, the various arguments put forward are not mutually exclusive. It is perfectly feasible, then, to endorse any number of the reasonings simultaneously. Nor are the arguments authoritative in the sense that, per se, they preclude certain forms of chimaera research from being ethically defensible if sufficiently powerful arguments so advocate. It is perfectly possible to embrace one or more of the reasonings, therefore, without thereby taking a definitive stance on the issue of whether manufacturing human-animal chimaeras is ethically wrong.

Members of the two councils attach varying importance to the arguments adduced. However, they all agree that a large part of chimaera research is located within a field where vigilance needs to be exercised. A good deal of chimaera research deals with changes to embryos and fetuses, and such changes will potentially be capable of affecting the germline and hence resulting in irreversible changes to future individuals. At the same time, we find ourselves in areas of research that are new and therefore characterized by the lack of knowledge concerning the long-term consequences of such interventions. That advocates proceeding with caution.

Further, all the members find experiments or therapies that result in crossbreeds of humans and animals unacceptable if they lead to the moral status of the individual in question being altered.

For some members the problematic issue resides in such changes violating the dignity of the individual in question. This might be the result if a basically human being had cells or organs from animals added in a way that diminished that being's cognitive characteristics. It might also be the result of a basically animalistic being having its cognitive characteristics—and hence its ethical status—enhanced, but not being treated in accordance with this enhanced ethical status.

For other members, it is significant that essential social practices depend on humans and animals still being identifiable as two clearly separate categories. There must be no way of doubt arising as to what ethical status to ascribe to a particular modified individual, and thus what debt of protection we owe that individual. In this connection it is also important that we are not placed in a situation where we are forced on occasion to assess ethical status at individual level instead of doing so according to the individual's affiliations with a particular species or group; for that will potentially open the way to being forced to reassess, for example, the ethical status of severely retarded people or certain higher-ranking animals.

Some members consider experiments or therapies capable of altering the brain, i.e. the cognitive characteristics, of animals and humans primarily capable of altering—or at any rate leading to doubt about—the ethical status ascribable to a particular modified individual, and hence what debt of protection we owe that individual. In the opinion of these members, therefore, experiments potentially capable of assuming such implications should not be performed.

Some members think that mankind has a special dignity, which will be violated by experiments producing crossbreeds extensively modified in relation to the

human baseline. Such experiments ought not to be permitted, therefore. The members find that human embryos are also covered by this dignity. It therefore follows from the view that experiments entailing comprehensive changes to human embryos will also constitute a violation of dignity for the human life in question, and that such experiments should therefore not be conducted.

Some members find that the question of which changes will be problematic to impart to a particular individual calls for a broader approach than considering just those that will cause the ethical status of the individual to be modified. Many other changes will be of importance to the identity of the individual in question; these might involve, say, marked changes in appearance. Some of these members refer here to the way such experiments will radically alter the prevailing natural order, pointing out that the consequences of doing so may become unmanageable. Experiments that can lead to the creation of such individuals should, in the opinion of these members, not be allowed to be conducted.

A single member feels, on balance, that the act of undertaking manipulations to humans and animals of the forms referred to should be discontinued.

Chapter 5
Recommendations

The Danish Council of Ethics and the Danish Ethical Council for Animals urge the legislators to take steps to adjust the legislation to take into account the developments that have happened within hybrid and chimaera research in recent years as described in this report.

With hybrid and chimaera research, it will potentially be possible to produce creatures that are difficult to place in biological, ethical and legal terms. The councils' members urge politicians to adjust the legislation in a timely enough fashion to prevent such creatures being formed.

The existing legislation is based on the fact that humans and animals are two separate categories, which can clearly be demarcated from each other and must be covered by different levels of protection. Thus there is a ban on creating a human embryo for research purposes alone and a ban on allowing crossbreeds to be born that can be labelled as human. Conversely, animal embryos can be created without consideration for the purpose, and as long as a resulting crossbreed can be characterized as an animal, there are no rules preventing it from being born. After birth, human beings are covered by far more extensive considerations of protection than animals, which may be included, among other things, in medical experiments associated with certain risks, the can be put down, kept as pets and eaten.

Potentially, some admixtures of animals and humans may be difficult to place into this legal framework. This is partly due to the law not defining when something is human. In the preceding, therefore, the councils have formulated some ideas as to when crossbreeds between animals and humans give rise to special ethical problems:

1. When the creatures created have been extensively modified with regard to their cognitive characteristics.
2. When created animal-human crossbreeds are so extensive that there may be doubt as to whether they belong to one species or another, including creatures that produce germ cells – and hence, in theory, offspring – of a species different to their own.
3. When the creatures created have otherwise had key species characteristics altered, many of the members also find it problematic, even where the cognitive characteristics are not affected and there is no doubt as to the species affiliation. They mention changes, for example, which, for ornamental purposes, impart animal attributes to humans. The greater part of these members, however, do not consider the problems to be such as to call for the need to be legislated against.

In Chapter 4 some arguments were adduced to show that experiments resulting in such ethically significant changes would also be ethically problematic to conduct. As was shown, the councils' members attribute varying weight to the different arguments put forward, consonant with their divergent views of what constitutes ethically significant changes.

The majority feel that none of the arguments adduced is so convincing as to advocate prohibiting hybrid and chimaera research altogether. Part of the research is unproblematic. For the research that can be claimed to be problematic, a majority feels that the ethical problems connected with carrying out certain of the experiments can and should be weighed against other considerations. Their possible damage must be viewed in relation to the benefits the experiments will be able to generate in the form of developing essential basic research or new therapies to combat severe disorders in humans and animals. Their potential usefulness may be a weighty argument. So even in those instances that can be problematic, based on the criteria listed, the convincing hope that such experiments can lead to new therapies being developed for severe

disorders may outweigh their problematic nature in some cases. Whether this is so will have to rest on a concrete assessment done on a case-by-case basis.

The majority of the two councils' members do not, therefore, consider that all the experiments in question to create crossbreeds should be banned a priori. But clear limits do need to be drawn up. The councils are agreed as to the intentions of the present legislation but find that the new research should give cause for some careful reviewing of the legal provisions on the basis of the ethical guidelines indicated here. Inter alia, the research legislation ought to be adjusted so that the relevant approval body is also granted the authority to reject experiments and trials that will potentially lead to the creation of crossbreeds between humans and animals (including fetuses) modified to an unacceptably high degree from an ethical standpoint. This may, for example, involve experiments which:

- crucially affects an animal's cognitive functions in a human direction (e.g. transfer of human embryonic or human neural stem cells to the brain of early fetuses or born experimental animals (particularly primates) or transplantation of parts of brains between animals and humans)
- could impact on a human brain in some way that reduces the cognitive capacities (transfer of neural stem cells from animals, or parts of animal brains to born humans for therapeutic purposes)
- could lead to the formation of human germlines in animals (e.g. by the transfer of human embryonic stem cells to early animal embryos or transplantation of human germline-producing tissue to animal fetuses or born experimental animals)
- could give rise to extensive mixtures between animals and people (hybrids or embryo fusion)
- brings into the world experimental chimeras or hybrids that have been so crucially altered that justified doubt can arise as to whether the crossbreed can still be classified as an animal and can thus be put down if the

experiment has an adverse outcome (e.g. when transferring human embryonic stem cells to early animal embryos)

- entails born crossbreeds being given an opportunity to multiply other than in closed systems, corresponding to what applies to experiments on genetically modified organisms, and thus pass on any changes in the gene pool to their descendants
- involves a chimeric experimental animal with the ability to form human germlines being permitted to multiply
- involves the implanting of a human embryo into an animal womb or of an animal embryo into a woman's womb.

The councils' members also wish to raise the question of whether the existing rewiev system will be suitable for handling this type of trial assessment. The system contain a clear-cut division: experiments that include human parts such as cells must be approved by a scientific-ethical committee, whereas experiments on animals must be approved by the Danish Animal Experiments Inspectorate. The councils deem it important to create a framework to enable the new experiments with crossbreeds to be subjected to overall evaluation in accordance with the recommended criteria.

It might also be an advantage if relevant ethical councils were heard when considering leading cases that go on to form a legal precedent.

Furthermore, the legislators ought to contemplate whether the present legal basis concerning the creation of crossbreeds between animals and human beings for research and therapeutic purposes is even appropriate altogether. As mentioned in Chapter 3, relevant legislation exists in a number of different laws; which, other things being equal, only serves to muddy the legislative waters and increase the risk of ethically unacceptable experiments or experimental therapies. In chronological terms, the legislation has been shaped in several stages and has had differing purposes, giving it the feel of a proliferation of "offshoots".

The members therefore recommend setting in motion deliberations as to whether the time is right to collate the legislation in the field, and in that connection to update it in those domains where progress in research has created a need to take on board the delineation of frontiers in keeping with ethical principles.

Odd members few?? of the two councils feel that manipulation of the forms of humans and animals discussed should cease entirely. Unless politicians are prepared to put in place a total ban, however, the members concerned can accept the proposal above as a step in the right direction.

Appendix.

Examples of scientific articles about animal-human hybrids and animal-human chimaeras

– focusing on changes in identifying organs and highly extensive mixtures of cells from animals and humans

An expert opinion drawn up by biologist Thomas R. Mikkelsen, MSc, PhD, in spring 2006

11 principal points

- There are published examples of cell nucleus transfers from human cells to animal ova (nuclear transplantation), incl. subsequent development to the blastocyst stage.
- There are a number of published examples of both stem cells from human embryos/fetuses and stem cells from adult human beings having been transplanted into animal embryos/fetuses.
- E.g., human embryonic stem cells have been transplanted into the brain of mouse fetuses, brain stem cells from human fetuses transplanted into the brains of both rat and macaque fetuses, and stem cells from adult humans' bone marrow transplanted into sheep fetuses.
- There are many published examples of both stem cells, tissues and organs from human beings (embryos, fetuses or born infants) having been transplanted into post-natal (born) animals.
- Among others, there are many published examples of stem cell transfers from the nervous system of human embryos/fetuses to animal brains or spinal marrow (mice, rats and monkeys).
- When human stem cells from the nervous system are transplanted into animal embryos, animal fetuses or born animals' brains or spinal marrow, the typical course is for the cells to establish themselves, differentiate into

nerve cells, among others, establish connections with the host animal's nerve cells, and possibly migrate and survive for a long time.

- Published examples of changes to identifying organs in chimaeras include a number of examples of human stem cell transplantation to the brains of animals/animal fetuses/animal embryos, animals that have had germ cell-forming cells or tissues from humans implanted, and animals that have had human skin transplanted.
- Published examples of highly extensive mixtures of cells from animals and humans in chimaeras include animals with a humanized liver and animals with a humanized immune system.
- There are published examples of cells, tissues or organs from animals having been put into human beings, including into the brain. The examples include transplantation of whole organs from animals, transplantation of pancreatic tissue from pigs and transplantation of neurons from pig fetuses into the brain of patients with Parkinson's.
- Published examples of animal-animal chimaeras of possible relevance to animal-human chimaeras include e.g. chimaeric animals made by transplanting parts of the brain between quail and chicken embryos, embryonic chimaeras between sheep and goats, and chimaeric animals that produce sperm cells from another species of animal in their bodies.
- No published examples have been found of actual hybrids between humans and animals (formed by the fusion of germ cells), transplantation of cell nuclei from animals to human ova, chimaeras of human embryos or fetuses with non-human cells, insertion of human embryonic stem cells into blastocysts from animals and human embryos inserted into an animal womb.

Animal-human hybrids

I have surveyed the literature far and wide during my searches. During those searches I have not come across very many examples of animal-human hybrids.

Thus I have not found any published examples of **”human ova fertilized with non-human sperm”** and **”human oocytes that have been enucleated and had a cell nucleus from a non-human cell substituted by nuclear transplantation”**. I should think this is because there are no examples of scientific articles on these subjects.

Under the category of **”non-human ova fertilized with human sperm”** one might possibly allocate the so-called ”hamster egg penetration test”, in which human sperm cells are examined for their ability to penetrate hamster eggs (Scottish Council on Human Bioethics, 2005). The sperm cells do not fertilize the hamster eggs, however, they merely (if at all) penetrate the egg cells, so there is no question of actual hybrids being formed.

Animal eggs whose cell nucleus has been replaced with the nucleus from a human cell (and similar experiments)

The category/example above contains a few, but by contrast very interesting examples. Chen et al. (2003) report, with a view to exploring the possibilities for producing cell and tissue for transplantation by transferring cell nuclei from connective tissue cells from the skin of both children and adult humans to rabbit egg cells. Before transferring the cell nuclei, the researchers had removed the egg cells’ own nuclei. Following transfer, the rabbit egg cells with human cell nuclei began dividing. They developed to the blastocyst stage in the space of 5-7 days. From specific cells in the blastocyst (the inner cell mass) the researchers isolated cells that were apparently stem cells, in that they were capable of differentiating (developing into specialized cells) into many different cell types, including nerve and muscle cells.

The Chinese researchers’ work is discussed in Abbott and Cyranoski (2001), inter alia, and also in the Scottish Council on Human Bioethics (2005). The latter

refers to Chen et al.'s article having been published in "a relatively minor and obscure journal".

Illmensee et al. (2006) describe similar experiments. They used egg cells from cows, fusing the (pre-enucleated) egg cells with cells from adult humans, partly granulosa cells from ovaries, partly fibroblast cells (connective tissue cells) from skin. Some of the bovine-egg human-cell hybrids developed to the blastocyst stage in the space of six days.

These are probably the experiments and results referred to in the Scottish Council on Human Bioethics (2005) as being "unpublished in any peer-reviewed journal". The experiments are alluded to (more superficially) in a "Commentary" by Zavos (2003), and Abbott and Cyranoski (2001) also mention such experiments.

White blood cells from adult humans have also been injected into egg cells from *Xenopus laevis* (an African clawed frog) to investigate how the genetic material is reprogrammed when cell nuclei are transplanted into egg cells (Byrne et al., 2003). This article makes no mention of the egg cells with the foreign (human) genes beginning to divide.

Hybrids of somatic cells (non-germ cells) formed in animals or humans

Several examples exist of human cells transplanted into animals, including animal embryos and fetuses, having apparently fused with the host animal's cells to some extent.

Ogle et al. (2004) investigated pigs that had had haematopoietic stem cells implanted, in the fetal state, from human beings. They found that human cells and pig cells had apparently fused in the chimaeric pigs, so that there were both "pure" human cells, but also human cells fused with pig cells present in the pigs.

In reality up to 60% of the human cells in the chimaeric pigs were cell hybrides formed through the fusion of human and pig cells, so Ogle et al. report. References to a number of examples of such fusions between somatic cells in chimaeric animals will be found in Ogle et al. (2005).

Animal-human chimaeras

Embryonic or fetal animal-human chimaeras

I have not come across published examples of "**chimaeras of human embryos or fetuses with non-human cells**", e.g. "**mixing of blastocysts from animals and humans**" or "**insertion of non-human stem cells into a human embryo or fetus**" during my searches. My assessment is that there is no published research belonging under these categories.

With regard to the category "**Chimaeras of non-human embryos and fetuses with human cells**" the matter takes on a different complexion. There are a large number of published examples of this type of research.

Human stem cells from embryos/fetuses transferred to animal embryos or fetuses

There are a number of published examples of different types of stem cells from human embryos or fetuses having been transplanted into the embryos or fetuses of animals. Some representative examples have been described below.

Mice

Moutri et al. (2005) transplanted human embryonic stem cells to the ventricles (fluid-filled brain cavities) of fortnight-old mouse fetuses in order to investigate the cells' ability to differentiate. Two months after the transplant the researchers found that the transplanted cells had differentiated into functional, active neurons (nerve cells) and glia cells (connective tissue cells in the nervous system). They also observed synapses (communication links) between cells of human

origin and the host cells, i.e. murine cells, in the mice's brains, and electrophysiological measurements showed that the cells were apparently functioning like normal neurons. Human-origin cells had been integrated into the mice's forebrain, though also into other regions and parts of the brain, including widely into the cerebral cortex, hippocampus, thalamus and cerebellum (little brain). Moutri et al. estimate that less than 0.1% of the brain cells in the chimaera mice are of human origin, and they observed no fusions between transplanted cells and host cells. Otherwise, having chimaera brains seems not to have had any consequences for the mice.

Rats

Brüstle et al. (1998) transplanted brain stem cells from 53 to 74-day-old human fetuses into the ventricles of 17 to 18-day-old rat fetuses in order to investigate how such stem cells move and differentiate in the brain. On examination one to eight weeks after the transplant, researchers found that the transplanted cells had been incorporated into many regions of the brain (including the cortex, hippocampus, olfactory nerve, hypothalamus and brainstem). The cells had differentiated into both neurons and astrocytes and oligodendrocytes (connective tissue cells in the nervous system). The researchers themselves use the expression "widespread CNS chimaerism" in their description of these chimaeric rats. Both Moutri et al.'s and Brüstle et al.'s results can be valuable in connection with the possible application of stem cells to treat neurodegenerative disorders of the central nervous system.

Sheep

A long string of experiments have been performed on the so-called "fetal sheep model of human stem cell transplantation". Here human cells are transplanted into sheep fetuses at a juncture in fetal development when the fetuses are still pre-immune, i.e. they have not developed the immune defence mechanisms that result in the rejection of such foreign cells. The transplanted cells develop and differentiate together with the ovine cells in the fetus, therefore, becoming part of

the sheep's body, integrating with different organs and tissues to varying degrees. One of the points of this type of experiment is to investigate the possibilities of using human stem cell transplantation as a form of therapy for disorders in which particular cells have been destroyed. The purpose of experiments on animals is partly to clarify how such stem cells develop following transplantation.

One example of this type of sheep-human chimaera has been made by implanting haematopoietic stem cells from human fetuses, more particularly from the liver of 12 to 15-week-old human fetuses, into sheep fetuses. Several years after the transplants, from very few percent right up to between 10 and 20% of the different blood cell types in the adult sheep were of human origin (Zanjani et al. (1995); Zanjani et al. (1996)).

A similar example is chimaeras formed by transplanting neural stem cells from human to ovine fetuses (Almeida-Porada et al. (1999); Almeida-Porada et al. (2005)). At birth (i.e. three months after transplantation) the transplanted human cells had developed into haematopoietic cells in the sheep's blood, bone marrow, liver, thymus and spleen. The experiment shows that stem cells from the human brain are capable of differentiating into haematopoietic (blood cell forming) cells. In similar experiments, mesenchymal cells from human fetal kidneys proved capable of developing into both blood cells and liver cells, but also into cells in the brain when transplanted into ovine fetuses (Almeida-Porada et al. (2002)). Here, then, the sheep formed were also chimaera in a number of different organs/tissues.

Goats

Haematopoietic cells from human umbilical cord blood (which I consider here, in other words, as fetal stem cells) have also been transplanted into goat fetuses, following the same method and with the same overall purposes as the experiments with sheep mentioned above (Zeng et al. (2005)). Here again, the cells turned out to establish themselves and develop into blood cells. Between

approx. 0.5% and 5% of the different types of blood cells in the goats' blood were of human origin for up to 16 months after transplantation. The researchers also found cells of human origin in the chimaeric goats' livers.

Monkeys

Ourednik et al. (2001) transplanted neural stem cells from a 15 week-old human fetus into Bonnet macaque monkeys (*Macaca radiata*) in order to investigate cell differentiation. 12 to 13-week-old simian fetuses had the human cells injected into the ventricles. After fetal development for a further 16-17 weeks the researchers investigated the chimaeric monkeys' brains. The injected human cells had divided, spread to large parts of the brain and differentiated into both neurons and glia cells. Researchers observed up to 100,000 or so cells of human origin per monkey brain. Here, then, we have a considerable number of human cells present in an "identifying" organ of another species. The human cells, however, make up only a negligible proportion of the total number of cells in the monkeys' brains.

Human adult stem cells transferred to animal embryos or fetuses

There are also a number of published examples of different types of stem cells being transplanted from adult human beings into animal fetuses or embryos. Some representative examples have been described below.

Sheep

The "fetal sheep model of human stem cell transplantation" described above has also been used to a great extent in connection with stem cells from adult human beings.

Almeida-Porada et al. (2001) describe e.g. how particular stem cells from bone marrow (marrow stromal cells, which can develop into bone, cartilage, fat and muscle cells, among others) from adult human beings developed into both

haematopoietic cells, liver cells and skin cells following transplantation to pre-immune ovine fetuses.

Transplantation of haematopoietic bone marrow cells from adults to ovine fetuses resulted in other experiments to develop blood cells of human origin as well as liver cells. Up to 20% of the total number of liver cells in these chimaeric sheep were of human origin (Almeida-Porada (2004)).

Mesenchymal cells from adult donor bone marrow (as well as from fetal brain and fetal liver) can also develop into (inter alia) cells in the heart's system of pathways following transplantation into the abdominal cavity of pre-immune sheep fetuses (Airey et al. (2004)). While examining the transplanted sheep fetuses at a late fetal stage, Airey et al. found that of the cells in the Purkinje fibres of the ovine cardiac ventricles (heart chambers) more than 40% were of human origin—in other words, another example of an organ in a chimaeric animal where a huge proportion of the cells present in part of the organ are human in origin.
Liechty et al. (2000) transplanted mesenchymal stem cells from adult humans' bone marrow into the abdominal cavity of pre-immune 65 day-old sheep fetuses. The transplanted cells established themselves and differentiated into cartilage cells, fat cells and heart muscle cells, among others, which were present in the chimaeric sheep for up to 13 months after transplanting. It is interesting, incidentally, that when Liechty et al. transplanted human cells to 85 day-old sheep fetuses, i.e. sheep fetuses that were no longer pre-immune, rather surprisingly, the transplanted human cells were also able to get established.

I have not come across published examples of research that fall under the category of "**Human embryonic stem cells inserted into blastocysts from mice...**", nor any examples in which human embryonic stem cells have been inserted into blastocysts from other animals, despite that kind of research having received a certain amount of publicity in different news media (see e.g. Scottish Council on Human Bioethics (2005)).

Born (post-natal) animal-human chimaeras

A great many examples of research have been published in which human beings have had cells, tissues or organs from animals transplanted into their body and in which animals have had cells, tissues or organs from humans transplanted into their body.
Typically, transplanting cells after birth will (presumably) not give the transplanted cells an opportunity to develop, spread and differentiate to the same degree as when transplantations are done to an embryo or fetus.

Human beings who have received cells, tissues or organs from animals

There are examples of whole organs being transplanted from animals to humans, e.g. kidneys from rabbits, pigs, goats and chimpanzees have been transplanted to humans on an experimental basis (Reemtsma et al. (1964)). Such experiments have been carried out in order to explore the possibilities of using animal organs for transplanting into humans. The person who received a chimpanzee's kidney survived for nine months (Ahn et al. (2004)). Other examples are transplantation of a heart from a baboon to an infant (who subsequently survived for 20 days) (Bailey et al. (1985); Walpoth et al. (1986)) and liver transplantation from baboons to humans. One patient survived with a baboon's liver for 70 days (Starzl et al. (1993); Collins (2003)).

By way of experimental therapy, neurons from pig fetuses have been transplanted into the brain of patients with Parkinson's (Deacon et al. (1997); Fink et al. (2000); Schumacher et al. (2000)). The neurons involved were from 27-day-old pig fetuses, injecting some 12m neurons per patient into the part of the patient's brain affected by Parkinson's. Some of the patients showed improvement after the transplant, with one patient surviving for more than seven months. On autopsying this patient, pig neurons were found that were producing dopamine (the neurotransmitter lacking in patients with Parkinson's), together with other neurons and glia cells that originated from the transplanted pig cells. The pig neurons had axons (stolons or offshoots on nerve cells) to other parts of the

patients' brains, and they showed signs of having moved after the transplant. What we have here, then, is chimaeric humans in whom an "identifying" organ has been modified.

Groth et al. (1994) describe the transplantation of pancreatic tissues from 66 to 81-day-old pig fetuses into kidney-transplantees with diabetes. The pancreatic tissue was either injected into the portal vein of the liver or positioned under the fibrous capsule of the kidney on the transplanted kidney. Researchers found signs of the transplanted pancreatic tissues functioning, as insulin and glucagon were being produced in the tissue.

Animals that have received cells, tissues or organs from humans

Mice

Kaufmann et al. (1993) describe the transplantation of pieces of human skin (from adults) slightly larger than 1 cm^2 onto the back of immune-defective mice. The skin here grows for more than a year without any problem. Mice with transplanted human skin can, according to Kaufmann et al., be used to investigate a number of physiological and pathophysiological dermal conditions. The skin might be regarded as an "identifying" organ, as it is an organ that has a particular, characteristic appearance in human beings.

Embryonic and fetal organs – stomachs, intestines, tracheas and lungs – from 6 to 10-week-old human embryos/fetuses have been transplanted into immune-defective mice with a view to being able to study how these organs develop. The organs developed into "micro-organs", and the chimaeric mice with human organs normally survive (Angioi et al. (2002)). Similar experiments and results have been described in Dekel et al. (2003) and Escotte et al. (2004).

In order to investigate the possibilities for treating type-1 diabetes by transplanting pancreatic tissue, Castaing et al. (2001) implanted embryonic pancreases from 6 to 9-week-old human fetuses under the fibrous capsule of the

kidney in immune-defective mice. The pancreatic tissue grew in the mice, insulin-producing cells developed, and these produced enough insulin to regulate the mice's blood sugar normally after their own insulin-producing cells had been destroyed.

In experiments described in Dandri et al. (2001) liver cells isolated from adult humans are transplanted to immune-defective and transgenic mice whose own liver cells (in the case of many of them) have been destroyed owing to the genetic structure that has been engineered into the mice's genetic material. The transplanted human liver cells invaded the mice's liver, in some mice comprising up to 15% of the total number of liver cells two months after transplantation. Researchers also found signs of the transplanted human liver cells being functional for at least two months. The purpose of these experiments was to create a mouse model that can be used for investigating liver disease in human beings, e.g. infection with hepatitis B-virus.

During similar experiments other researchers have achieved virtually complete "humanization" of the mouse liver.

Tateno et al. (2004) used liver cells from a number of human donors (youngest donor: 3; eldest donor: 61 years of age), and in some of the chimaeric mice the researchers produced by transplanting these liver cells, approx. 80% of the liver cells were of human origin. Katoh et al. (2005) also achieved a very high degree of humanization of the liver in mice (up to 90%) by injecting liver cells, isolated from children, into the spleen of 20 to 30-day-old immune-defective mice. Similar experiments are discussed in Nishimura et al. (2005). These chimaeras may be said to fall under the category of "highly extensive mixtures of cells from animals and human beings" – in terms of the liver, at any rate.

Thymus, liver, lymph nodes and spleen from human fetuses have been transplanted into immune-defective mice, and in this way mice with a "humanized" immune system have been developed—or in short: mice with a

human immune system (McCune et al., 1988). Such mice can be infected with HIV (Namikawa et al., 1988) and thus provide important knowledge about the HIV infection's development and possibilities for fighting HIV. This is another example of an extensive mix of cells from humans and animals, with large parts of an entire organ system in an animal being human. Several examples of this type of research will be found in Thomsen et al. (2005).

A number of experiments have been carried out in which human ovaries were transplanted into mice (see Aubard, 2003). They were either transplanted to the fibrous capsule of the kidney or positioned under the skin of the mouse, but the human germ cells were separated, in other words, from the mouse's own reproductive apparatus. Examples have been seen of some follicular development, but there are no examples of mature human egg cells, capable of fertilizing, developing in such chimaeric mice.

Experiments have also been conducted that involve transplanting cells able to develop into sperm cells (spermatogenic cells), from human testicles. Reis et al. (2000) describe experiments in which such cells are injected into the testes of, inter alia, immune-defective mice. The researchers did not, however, observe implantation of the transplanted cells when they examined the mouse testes up to 5 months after the transplant, and hence no development of finished human sperm cells either. But if the experiment had succeeded, the mouse testes could presumably have generated both human and mouse sperm cells. If it does become possible to ”produce” human sperm cells in animals, it may possibly be a relevant form of treatment for some infertile men.

Galli et al. (2000) describe experiments in which neural stem cells from human embryos develop into skeletal muscular cells when injected into the leg muscle of a mouse—a muscle that is in the process of regenerating after an induced injury. These experiments demonstrate the great plasticity of stem cells.

Coles et al. (2004) describe isolating stem cells from a retina taken from adult humans' eyes. They transplant such cells to the eyes of newborn, immune-defective mice (as well as embryonic (day 3-4) chickens) in order to investigate the stem cells' developmental potential. In the mice the transplanted human cells then differentiate so that there are human-origin photoreceptors (cones and rods) in the chimaeric mice's eyes after 28 days, i.e. mice seeing partly with the aid of human cells.

Transplants to brain or spinal marrow

Transplants of human cells to brain or spinal marrow on animals are typically done with a view to either investigating stem cells' developmental potential in general or investigating the scope for using stem cells specifically for treating particular injuries of the brain or spinal marrow where cells have been destroyed or have died.

Human neural stem cells from both brain and spinal marrow have been transplanted to the ventricles of newborn immune-defective mice. The transplanted cells establish themselves, divide, migrate and differentiate, and they can be observed until at least 12 months after transplantation (Uchida et al. (2000)). Zhang et al. (2001) also transplanted neural stem cells, developed from human embryonic stem cells, into the ventricles of newborn mice. During subsequent examinations of the mice's brains a few weeks after transplantation, researchers found cells of human origin in a number of different regions of the brain. The cells had differentiated into neurons and glia cells.

Imatola et al. (2004) transplanted human neural stem cells from fetuses into the brains of mice with an induced injury inflicted on the mice by interrupting the blood supply to a particular area of the brain. The cells were transplanted to an area slightly away from the damaged one, and researchers observed that the transplanted cells migrated towards the damaged area.

Neural stem cells from human fetal brains have also been transplanted into the spinal marrow of immune-defective adult mice with induced injuries to the spinal marrow (Cummings et al. (2005)). The transplanted cells survive, migrate and differentiate into nerve cells and connective tissue cells in the nervous system. The mice with transplanted cells show improvements in their motor skills, indicating that the transplanted cells are functional and can partly repair the induced injury to the spinal marrow. Synapses are observed between human and murine cells in the chimaeric mice's spinal marrow. In addition, some of the transplanted cells form myelin sheaths (isolating layers) around neurons in the mice's spinal marrow. Similar experiments have been conducted by Stepanov et al. (2003).

Rats

Transplants to brain or spinal marrow
Svendsen et al. (1997) transplanted stem cells from the brain of a 22-week-old human fetus into rats. The rats had been pre-inflicted with an injury in the part of the brain that does not function correctly in patients with Parkinson's, in order to thereby produce a rat model of the disease. The transplanted cells were inserted into the injured part of the rats' brains, and researchers observed that the cells differentiated into both neurons and connective tissue cells. Some of the rats showed signs of improved function of the injured part of the brain.
In another rat model for Parkinson's, where the normal dopamine-producing neurons had also been destroyed, Park et al. (2003) implanted genetically modified embryonic human stem cells that produce dopamine as a result of the genetic modification.

Two to six weeks after transplanting the human cells into the damaged area of the rats' brains, the rats showed signs of improved function in the area.

Armstrong et al. (2000) transplanted neural stem cells from 9-week-old human fetuses to the brain of rats that had been pre-inflicted with damage in the region

of the brain affected by Huntington's. The purpose was to investigate the possibilities for using stem cell transplantation to treat Huntington's. Each rat was infused with between 800,000 and 1,000,000 human cells, and the transplanted cells developed into neuron-like cells with offshoots to different parts of the brain.

It has also been attempted to inject other types of cells from humans into the central nervous system of rats. Saporta et al. (2003) injected leukocytes and haematopoietic stem cells from cord blood into the spinal marrow of rats with induced spinal marrow lesions in order to investigate these cells' potential for development and differentiation. Some of the rats that had human cells implanted did improve—despite the fact that no neural cells were involved.

Kelly et al. (2004) transplanted neural stem cells from 16 to 20-week-old human fetuses into the cerebral cortex of adult rats seven days after the rats had been inflicted with an injury in a particular part of the brain by interrupting the blood supply. The transplantees survived (at least) four weeks after the transplant, and researchers observed that the transplanted human cells migrated in the direction of the induced brain injury. The transplanted cells developed into cells with neuron characteristics.

Monkeys

Transplants to brain or spinal marrow
Iwanami et al. (2005) transplanted neural stem cells from 8-week-old human embryos/fetuses into the spinal marrow of adult marmosets (*Callithrix jacchus*). The monkeys had been pre-inflicted with an injury to the spinal marrow, and the cell transplant was effected in the damaged area.
Eight weeks after the transplant the transplanted cells turned out to have differentiated into neurons and astrocytes and oligodendrocytes (connective tissue cells in the nervous system), and the monkeys were showing motor

improvements. This suggests that the transplanted, differentiated neurons are functional in the chimaeric monkey brains.

Researchers have also done experiments involving cell transplantation to the CNS of African green monkeys (*Chlorocebus aethiops sabaeus*). Bjugstad et al. (2005) wished to investigate the possibilities for using stem cells to treat Parkinson's. First, therefore, they chemically destroyed the dopamine-producing neurons in the green monkeys' brains with a view to creating a simian model for the disorder. Then they transplanted the neural, pluripotent stem cells from a 13-week-old human fetus into the destroyed areas of the monkeys' brains. After 4 and 7 months there were effects indicating that the implanted cells were functional and had partly taken over the destroyed dopamine-producing neurons' functions in the chimaeric monkey brains.

I have not come across published examples of "**Human embryos having been inserted into an animal womb**". In my opinion, this is because there are no such examples.

Animals with human chromosomes

One form of animal-human mixture that apparently falls outside the hybrid and chimaera categories is animals with human chromosomes. O'Doherty et al. (2005) describe a mouse with a (virtually) complete human chromosome no. 21. The mouse was developed in order to explore the chromosomal deviation in humans where there is an extra copy of chromosome no. 21, Down's syndrome. The mouse was made by transferring the human chromosome to embryonic stem cells and subsequently injecting these embryonic stem cells into early mouse embryos. The mouse has several Down's syndrome characteristics. Incidentally, many animals, primarily mice, have been produced that have one or more human genes integrated into their genetic material.

Animal-animal chimaeras

There are a number of published examples of interspecific animal chimaeras, i.e. animals that consist of crossbreeds of cells from two different species.
Fehilly et al. (1984) describe the production of embryonic chimaeras between goat and sheep. These chimaeras were produced by mixing cells from very early goat and sheep embryos at a point when these had only developed into the 4 to 8-cell stage. The chimaeric embryos were subsequently inserted into either sheep or goat surrogate mothers and developed into adult chimaeric animals with characteristics of both goat and sheep. Experiments with such chimaeras can, according to Fehilly et al., lead to a better understanding of the mechanisms that normally prevent species crossbreeds, and how cellular differentiation takes place during fetal development.

Similar experiments and results are described by Polzin et al. (1987). Other examples of interspecific animal chimaeras (referenced in Polzin et al.) are chimaeras between different species of mice (genus: *Mus*) and different species of cattle (genus: *Bos*).

A good deal of research has been done on post-natal chimaeras between chicken and quail—research whose purpose is partly to investigate the way the brain develops and functions. For example, experiments have been conducted in which particular parts of the brain in quail embryos are transplanted into the brain of chicken embryos. The chickens that do develop have chimaeric brains and display quail-specific behavioural traits (see e.g. Balaban et al. (1988), Balaban (1997) and Long et al. (2001)). This illustrates that by transplanting brain tissues, changes can be effected in identifying behaviour.

Gahr (2003) describes experiments whose purpose is to investigate the interaction between the brain and the sex hormones during quails' fetal development and the importance of this interaction for later sex-specific behaviour. Amongst others, Gahr carried out experiments in which he transplanted part of the brain from female quail embryos over to male quail embryos. The male quails with partially

female brains that developed from these transplanted embryos did not display the sexual behaviour typical of male quails.

Transplanting testicular tissues from one animal species to another is described in several published articles. Honaramooz et al. (2004) implanted testicular tissues from sexually non-mature rhesus-monkeys (*Macaca mulatta*) under the skin of immune-defective mice in order to investigate testicular development in primates, including the possibilities of remedying infertility in men. The transplanted testicular tissue grew and developed in the mice, and rhesus monkey sperm cells capable of fertilization were produced in the tissue. Snedaker et al. (2004) describe implanting testicular tissue from cats (sexually non-mature 1 to 5-week-old kittens) under the skin of immune-defective mice. Here, too, after 36 weeks' development, functional feline sperm cells are produced in the transplanted tissue. Snedaker et al. further refer to similar experiments with testicular tissues from pigs and goats.

According to Hochepied et al. (2004) so-called germline-competent ES cells had successfully been produced by 2004, i.e. embryonic stem cells able to contribute to the formation of germ cells when introduced into early embryos (from the same species!), from only one species, i.e. *Mus musculus* (house mouse). This shows that getting embryonic stem cells to contribute to the germline is evidently not that straightforward. And that underpins a supposition that it is bound to be even more difficult where embryonic stem cells from an entirely different species are involved, i.e. in interspecific chimaeras.[54]

[54] Comment from Professor Poul Maddox-Hyttel, KVL: As far as I know, it is only in mice that pluripotent ES cells (used to insert into blastocysts during chimaera production) have given rise to spread to the germline. In pigs and cattle, chimaeras have been produced from ES-like cells, but without spreading to the germline. To my knowledge, therefore, no interspecies chimaeras exist in which ES cells have given rise to the formation of gametes.
Comment from Ernst-Martin Fuchtbauer, Molecular Biology, University of Aarhus: So far there is only one species with germline-competent ES cells, which is the mouse. (Humans not tested, of course). So if one wants to find interspecies germline chimaeras, the obvious thing would be mouse ES cells in rat blastocysts, which to my knowledge does not work (but has been tried).

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Chapter 2 and appendix

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Chapter 3

Chapter 3
The Council of Europe's convention of 4 April 1997 on the *Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine.*

The Council of Europe's Convention of 18 March 1986 on the *Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes.*

Danish Act No. 402 of 28 May 2003 *on a Scientific-ethical Committee System and the Handling of Biomedical Research Projects,* with subsequent amendments.

Danish Consolidated Act No. 923 of 4 September 2006 *on Assisted Reproduction in connection with Medical Treatment, Diagnosis and Research etc.*

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Summary

The ethics of human–nonhuman chimera research

Chimeras are created in several fields of research, most commonly in connection with stem cell research. A chimera is an organism in which one animal's own cells and that of another are present side by side in the same body. A related organism is a *hybrid,* in which genetic material from animals of different species is present in each individual cell. These can be formed by fusing germ cells from animals of different species.

Some types of research on chimeras imply the mixing of cells from humans and nonhuman animals. This could give rise to ethical concerns for several reasons. One important reason is that the boundary between humans and animals is fundamental in our everyday practices, in society and in current legislation. Therefore, the Danish Council of Ethics and the Danish Ethical Council for Animals formed a joint working party in 2006, which is now finishing its report on ethical aspects of human-animal chimeras.

The following example illustrates some of the commonly accepted moral and legal distinctions between humans and animals:

Animals	Humans
Not legal entities	Legal entities
Can be owned by others	Cannot be owned by others
No right to respect of autonomy	Right to respect of autonomy
Can be killed and eaten	Can neither be killed nor eaten

Current Danish legislation

These distinctions are reflected in current Danish regulation of research on human subjects and research on live animals. The level of legal protection depends greatly on whether the research involves human subjects or animals.

One limit to experiments for which permission may be granted in accordance with Danish legislation is that animals must not be created in such a way as to render the human aspect prominent. Thus it is forbidden to develop and create a human being that is part animal. However, the law does not define when a creature can be termed human in more detail and provides no directions as to whether this should be determined in accordance with qualitative or quantitative criteria. Conversely, there is no ban on creating an animal that has been partly humanized. One extreme limit is that the animal must not be subjected to the experience of severe pain, other intense suffering or intense fear.

Where germlines, embryos or embryonic stem cells are involved in the experiment to mix human and animal components, there are narrow constraints on what can be permitted under Danish legislation. A human embryo must not be formed for research purposes alone. A human embryo may only be kept alive outside a woman's uterus for 14 days and a modified embryo must not be implanted into a woman's womb. A human embryo must not be implanted into an animal womb. These limits do not apply to early animal life.

The legislation contains no ban on humanizing a born animal, just as there is no ban on transferring animal components to a born human. According to the Danish legislation on animal experimentation an animal must not be subjected, in the process, to severe pain, other intense suffering or intense fear, whereas in the case of human beings there is a broad range of rules protecting a person's physical and mental integrity.

Thus current regulation expresses a clear-cut distinction between human beings and animals without actually defining what constitutes a human being. The

ongoing research on human-animal chimeras and hybrids has, however, generated a need for some definition and for argument to support this distinction between human and nonhuman animals, respectively.

Ethical considerations

The moral difference in our treatment of humans and nonhumans is sometimes justified by reference to the unique moral status we generally assign to humans. Two types of arguments are usually given in further support of this:

Humans are characterized by certain cognitive capabilities that should be valued and protected – e.g. the ability to act intentionally, engage in complex communication and speech, act for moral reasons and develop world views. The same capacities are at the core of the notion of human dignity. The problem with ascribing moral status to humans on the basis of their possession of high-level cognitive capacities is that many humans such as newborns, mentally impaired or demented individuals clearly lack these capacities. So should these individuals have moral status equal to normal adult humans?

Humans have their moral status simply because they belong to a distinctive species, *homo sapiens*. This view can be based on the belief that God created a certain order in the universe and gave man, as created in His image, a special status. For man to impose radical changes in the species God created would be morally wrong and tantamount to committing hubris.

This view raises difficult questions about the amount of human material an individual needs in order to be a human being. Should an organism with some human and some nonhuman cells and organs still be considered human?

Morally significant changes

It seems clear, though, that under both the cognitive-capacity and the "creational" views of moral status, uncertainty might arise as to which moral status should be assigned to certain human–nonhuman chimeras. In the report attention is therefore focused on:

- Chimeras in which extensive changes have been introduced in areas that may affect their cognitive capacities
- Chimeras in which the mixture of human and nonhuman cells is so extensive that confusion might arise as to which species the chimeric individual belongs to. This includes chimeras which might produce germ cells from a species different to their own.

A literature search was performed in order to investigate whether any parts of the chimera research presently being conducted could potentially lead to the creation of individuals that were changed in morally significant ways.

What kind of research is being done into human-nonhuman chimeras or hybrids?

Chimeric organisms can be created prenatally or postnatally. The **prenatal** method is likely to be the most extensive. In this strategy, which is of special interest to basic biology, human stem cells are introduced into embryonic or fetal animals, usually with the aim of exploring the stem cells' developmental potential (their pluripotency). In the **postnatal** strategy, stem cells, tissue or organs are introduced into developed (postnatal) animals with some disease or impairment. This can be done in nonhuman animals in order to test the therapeutic potential of stem cells for humans with certain diseases or impairments. Or it can be done in humans to treat e.g. neurodegenerative diseases (e.g. Parkinson's and Alzheimer's diseases) with cells from nonhuman animals.

Three possible types of research were identified that could potentially change the resulting individual in ways which, in a non-trivial sense, would affect the individual's identity or moral status if the transplantation was performed between humans and nonhuman animals:

- Research involving transplantation of human embryonic stem cells or neural stem cells to the brain of embryonic, fetal or postnatal nonhuman animals (particularly primates), or where parts of brains would be transplanted between humans and nonhuman animals (particularly primates).

- Research in which germline-producing tissue or embryonic stem cells are transplanted to early embryos in a way that might affect the germline. This could potentially lead to the production of human embryos in animals or animal embryos in humans.

- Research in which extensive mixtures were created, e.g. through fertilization of germ cells from humans and nonhuman animals (hybrids) or by embryo fusion of blastocysts from humans and nonhuman animals.

Would changing an individual's moral status be problematic?

But even if such research were performed and even if it did result in the creation of individuals with significantly altered moral status, why would this be morally problematic? Six types of arguments were considered:

The creation of chimeras is wrong if it violates the God-given dignity of humans or nonhuman animals. This could be the case if a human life is changed so extensively that the resulting organism is no longer clearly human. The difficulty concerns detecting how extensive the change needs to be in order for the human life to stop being human.

The creation of chimeras is wrong if it undermines the natural order of things. Anthropocentric insolence has led to the present situation where nature is threatened by human activity that does not recognize the innate wisdom of natural order. Again the difficulty lies in distinguishing ethical from unethical interventions into the natural order.

Risks and scientific uncertainty. Human beings do not have the knowledge to foresee all possible consequences of performing radical interventions in nature. This is a problem especially in areas where the interventions affect not only the chimeric individual but possibly also its germline, thereby potentially passing the changes on to future generations. This calls for extensive caution when carrying on chimera research.

The creation of chimeras is wrong if it denigrates the human dignity of the resulting being. This could be the case if an originally human being was altered in a way that reduced its cognitive capacities; or if an animal had its cognitive capacities enhanced but was not treated in accordance with its enhanced moral status.

Chimeras would violate the moral taboo against mixing humans with nonhumans. Taboos have an important function in guarding important social values, of which the prohibition against mixing humans with nonhuman animals is one. It is disputed, however, whether taboos should be seen as historical and cultural categories that can lose their foundation, and thus whether taboos against human-nonhuman chimeras are actually changing today.

Human-animal chimeras would introduce severe moral confusion. The creation of individuals that might not fit into any of the existing categories would force us to realize that we assign full moral status to human individuals that lack the capacities we associate with human beings, and not to higher animals which possess many of these capacities. But were we to change this and assign moral

status to individuals rather than to members of certain species the consequences for social practices where absolute respect for human life and integrity is a key element would be extensive.

Recommendations

The members give different weight to these arguments but find that none of them rules out every creation of human–nonhuman chimeras. There is, however, a need to modify current regulation to ensure that chimeras difficult to place biologically, ethically and legally will not be created. Thus the Council members agree that research should not be allowed if it e.g.:

- crucially affects an animal's cognitive functions in a human direction (e.g. transfer of human embryonic or human neural stem cells to the brain of early fetuses or born experimental animals (particularly primates) or transplantation of parts of brains between animals and humans)
- could impact on a human brain in some way that reduces the cognitive capacities (transfer of neural stem cells from animals, or parts of animal brains to born humans for therapeutic purposes)
- could lead to the formation of human germlines in animals (e.g. by the transfer of human embryonic stem cells to early animal embryos or transplantation of human germline-producing tissue to animal fetuses or born experimental animals)
- could give rise to extensive mixtures between animals and people (hybrids or embryo fusion)
- brings into the world experimental chimeras or hybrids that have been so crucially altered that justified doubt can arise as to whether the hybrid creature can still be classified as an animal and can thus be put down if the experiment has an adverse outcome (e.g. when transferring human embryonic stem cells to early animal embryos)

- entails born hybrid creatures being given an opportunity to multiply other than in closed systems, corresponding to what applies to experiments on genetically modified organisms, and thus pass on any changes in the gene pool to their descendants
- involves a chimeric experimental animal with the ability to form human germlines being permitted to multiply
- involves the implanting of a human embryo into an animal womb or of an animal embryo into a woman's womb.

Whether a specific research project will conflict with these recommendations should be assessed by a research ethics committee in each separate case. This implies an adjustment to the law, since the current Danish legal framework does not take sufficient account of research which combines elements from human and nonhuman animals.

The members therefore recommend that existing regulation be revised on the basis of the ethical principles laid out in the report. This would imply that the accreditation scheme is adjusted and committees are given a mandate to decline research projects that will potentially lead to the creation of human–nonhuman chimeras (including fetuses), which from an ethical viewpoint are altered to an unacceptable degree, as in the above-mentioned examples. The members also suggest that politicians consider whether it would be desirable to combine the assessment of research involving elements from animals as well as humans in one review body.