

Human Genetics Alert response to Science and Technology Committee Inquiry on Hybrid Embryos

Summary

Human Genetics Alert is a secular watchdog group which is not opposed to research on embryos or embryonic stem cells. We would support a ban on the creation of animal/human hybrid embryos for the following reasons: (1) the proposed experiments are of little scientific value; (2) we oppose the creation of embryos purely for purposes of research and (3) the strong public concerns about the unnaturalness of creating human/animal hybrids is valid and must not be ignored. Banning such research would have a positive effect upon UK stem cell research, since scarce research funding and the time of top scientists would not be diverted onto research of very little value. In its report, we urge the committee to present a more balanced and accurate account of the proposed research than the misleading account its proponents have put forward, and to move the ethical debate on the status of embryos on to the ethical middle ground upon which the law is based.

1. Introduction

Human Genetics Alert (HGA) is an independent secular watchdog group. We are not opposed to research on embryos or embryonic stem cells.

The author of this submission, Dr David King, is the Director of HGA. He is a molecular biologist who has been working for the past 16 years on ethical and social issues raised by genetic and reproductive technologies.

2. Scientific issues

2.1 Misleading descriptions

We are very concerned by misleading descriptions of these experiments which have been made by the scientists themselves and cannot be blamed upon the media. An egregious example of this is the suggestion that 'these cells are 99.5% human and not .5% animal', which is no doubt intended to suggest that the fact that their cells are inter species hybrids is only marginally relevant, and that biologically they will be practically identical to human cells. This is based on the grossest form of genetic reductionism i.e. the assumption that the biological characteristics of the cells can be read off simply from the respective proportions of DNA from the different species. In fact, at least up to the blastocyst stage the vast majority of mass and volume of the embryos will be of bovine or rabbit origin.

Crucially, the statement ignores the interaction between cytoplasmic factors in the cow eggs and the human nuclear DNA, which is essential for the correct reprogramming of the human nuclei to begin embryonic development. As we will discuss below, it is very unlikely that correct reprogramming will occur. So, in reality, the fact that these are inter species hybrids is crucially relevant to the likely success of the experiments. It is difficult to avoid the conclusion that scientists who know much better than this have intentionally misled the public in order to to emphasise the likely success of their experiments and to suggest that concerns about the unnaturalness of creating interspecies hybrids are misplaced.

An even worse example of misleading language occurs in the letter to the Times, which refers to animal eggs as 'the activating casing for cloned human embryos'. Here, the genetic reductionism is so extreme that the egg cytoplasm is nothing more than 'casing', and the emphasis on the importance of the nuclear DNA is so

great that it is seen to actually make the embryos simply human, rather than interspecies hybrids. Again, the calculated effect is to dismiss concerns about the unnaturalness of interspecies hybrids.

The Committee should also noted that the expected 'humanisation' of its mitochondria are a PROBLEM, for the stem cells, not, as has been suggested, a solution. As the human nuclear genome becomes active, it will produce many proteins which will migrate to the animal mitochondria, producing mitochondria with mixed species proteins. It is very likely that the human proteins will interact improperly with the animal proteins, thereby rapidly killing off mitochondria which produce the cell's energy. It is likely that this is a major source of the poor viability of such subcellular hybrids.

It is unfortunate that the scientists have not put any detailed account of the scientific rationale of their experiments into the public domain, let alone any attempt to deal with the very serious (and obvious) defects of their plans. Instead, the the public is presumably supposed to judge whether these experiments are worthwhile simply on the basis of trust in famous scientists. We expect that the many senior scientists who signed a letter to The Times in support of their publicity campaign have not seriously looked into the details of the planned experiments: instead, as is sadly too typical of the debate in this country on stem cell research, they will have signed the letter on the basis of their general support for scientific research and their disdain for what they see as woolly-headed and probably religiously-based ethical concerns. We therefore see the need to enumerate a number of the serious scientific defects of these experiments, in order to encourage an informed debate about their merits.

2.2 Scientific defects of the proposed research

2.2.1 Likelihood of obtaining embryonic stem (ES) cell lines

As far as we are aware there are no authenticated reports of cloned human ES cell lines, and only one report of ES cell lines from interspecies hybrids. Various laboratories around the world have been attempting to create such embryos and stem cells for at least eight years, and as far as we know this effort has produced only one, unreplicated published report of success. Despite considerable effort, it appears very difficult to obtain ES cell lines from cloned human embryos. It is certainly to be expected that the efficiency of obtaining stem cell lines from cloned interspecies hybrid embryos will be even lower. Yet in order to achieve statistically significant results in their experiments it will be necessary to obtain at the very least five experimental and five control cell lines for each condition to be studied.

The low efficiency of obtaining stem cell lines from cloned embryos derives, of course, from the unnaturalness of nuclear transfer which requires the complete reprogramming of differentiated cell nuclei to an embryonic state. We question whether a useful strategy for dealing with this problem is to make the problem even more difficult by making interspecies clones in which the cytoplasmic factors and their nuclear correlates will probably be mismatched. This is a strategy of simply applying brute force (i.e. creating huge numbers of embryos due to the easy availability of bovine and rabbit eggs). In our view the lowered efficiency of interspecies hybrids is likely to mean that that the scientists will waste a huge amount of time creating thousands of embryos with very little positive results. If these scientists must insist on using nuclear transfer, their time would be better employed in studies of the mechanism of reprogramming, in order to improve its efficiency.

It is instructive to compare conventional genetic engineering with the creation of subcellular hybrids. It is now well known and that genetic engineering of a single gene often fails because the gene disrupts chromosome stability, or is 'silenced' by the host genome, or the protein disrupts cellular metabolism or other structures. In the proposed experiments, the scientists are hoping for hundreds, maybe thousands of cross-species molecular interactions, between both the mitochondria and cytoplasm of the egg and nuclear genes and

proteins to work perfectly, in order to produce a normal cell. In our view, it is optimistic in the extreme to expect this to work.

2.2.2. Embryonic stem cell lines from cloned interspecies hybrid embryos will be abnormal

Even if ES cell lines can be obtained from hybrid embryos it is almost certain that they will contain subtle abnormalities in gene expression which will invalidate any experimental results obtained with them. It is now well established that cloned animals are abnormal due to genetic and gene expression defects, and it is to be expected that these gene expression defects, which result from incomplete reprogramming of the nuclear DNA will be present in any stem cell lines derived from cloned embryos. We are aware that there is some evidence that it is possible to obtain some cloned stem cell lines which appear normal: however, the burden of proof must remain upon those who seek to claim that all such stem cells are normal.

These abnormalities resulting from nuclear transfer will undoubtedly be compounded by further errors and abnormalities resulting from the interspecies mismatch, and from the presence of animal mitochondria. Even worse, it appears that each cloned stem cell will have a different set of gene expression abnormalities. Overall, these experiments are likely to be a study primarily of artefacts. Patient organisations would be wise to treat results from them with great scepticism.

2.2.3. Necessity of this research

Apart from the methodological problems mentioned above, the usefulness of these experiments is highly questionable.

The experiments proposed by the Edinburgh and London groups aim to investigate early molecular events in the aetiology of late onset conditions which will not manifest symptoms for several decades. It seems quite unlikely that any relevant events will be manifested within the time period that it is possible to culture stem cell lines without accumulating chromosomal and other abnormalities. Researchers into Motor Neurone Disease already have at their disposal a mouse model containing SOD1 mutations which would appear to be perfectly suited to obtaining the kind of data that these researchers seek.

The experiments proposed by the Newcastle group appeared to be aimed at developing the methodology for so-called 'therapeutic cloning'. It is now accepted by most researchers (including Professors Wilmut and Austin Smith) that the scenario of 'therapeutic cloning' as a widely used treatment for disease. is highly unlikely to ever be realised. Biomedical companies are not pursuing this solution partly because of the epigenetic defects caused by cloning, and partly because it would be absurdly expensive, and would only be available to the rich. It would also be highly impracticable, requiring the acquiring of expertise in embryo manipulation and tissue culture in each hospital. There would be further major problems with quality control for individualised batches of tissue. Instead, biomedical companies are pursuing alternative approaches to the problem of immune rejection of tissue.

Finally it must be noted that, the target of the Newcastle experiments, type 1 diabetes, can never be a candidate for treatment by this method, since it is an autoimmune, not a degenerative disease. Any transplanted tissue will be destroyed by the patient's immune system in the same way that he is his/her own tissue was in the first place.

Summary of scientific issues

Reporting and public debate on these issues has been based upon an assumption that the proposed research is of high quality and likely to produce important data which could contribute to cures for

serious diseases. In our view, because of the the methodological problems inherent in creating cloned interspecies hybrids and other problems with the experimental designs, this is very far from true. Whilst there are always uncertainties in medical research, these experiments must be viewed as extremely long shots. The responsibility for such misrepresentation must rest squarely with the scientists and their publicists, who, as we have shown above seem to have no scruples about using language which obfuscates the nature of the embryos being created and to minimise the methodological problems. This is disappointing but not shocking: experience with the stem cell debate for the last eight years has shown such linguistic manipulations and misrepresentations of science to be the norm rather than the exception. However, it is the role of the Science and Technology Committee not to be taken in by such misrepresentation and to present a more balanced account of the science as a basis for ethical discussions.

3. Ethics

A crucial question in deciding whether the proposed research should go ahead is the ethical status of the embryos created. It is a completely unsatisfactory situation that the debate in Britain has become polarised between scientists, who view the embryos as having no moral status and pro-lifers who view the embryo as a person, whereas the law is based on a compromise position, which views the embryo as a morally significant entity, which must be treated with respect. As a result there is very little debate on the ethical middle ground, which HGA supports and which is supported by the majority of the UK population. It is the duty of the Science and Technology Committee to restore the debate to this middle ground. Those who are not pro-lifers are not absolved of the duty of thinking about the ethics of manipulating embryos.

The question of the moral status of embryos created by these experiments is complicated by their inter-species nature. It is certainly questionable whether scientists should be permitted to create entities whose ethical status is uncertain. However, in our view, they must be treated as human embryos for the purposes of ethical discussion, for the following reasons. Firstly, as the scientists argue that they are sufficiently biologically equivalent to human embryos for valid medical research to be conducted on them. Secondly, the HFEA has concluded that they fall under the HFE Act. Thirdly, although it would be completely unethical to do this, if such embryos were implanted and brought to term, it seems probable that the resulting creature would be enough like a human being to claim legal personhood. If that is so, it follows that we should treat the embryos as a human embryo, from an ethical point of view.

If that is the case, then these experiments raise important ethical issues, since they would create an embryo purely for the purposes of research. We do not believe that embryos are persons with a right to life. However, UK law is based on the concept that embryos are morally significant entities and must be treated with respect. We believe that the creation of embryos purely as a source of biological raw material and as a means to an end (as a tool for research), and not for the purpose of reproduction, fails to respect their moral status. It is this view of the embryo as a mere thing which underlies efforts by companies to obtain patents on embryos as, in patent parlance, 'compositions of matter'.

This distinction between the use of surplus embryos and the creation of embryos purely for research is widely recognised around the world. Although there are many countries which allow embryo research, the UK is one of only five countries worldwide which permits the creation of embryos purely for research, and we understand that even here, it is done very rarely.

We recognise that there may be different opinions on this issue, which has barely been discussed in the UK. We urge the Science and Technology Committee to discuss this issue and not to fall into the usual polarised stalemate.

4. 'Unnaturalness'

A dominant theme in the public reaction to proposals to create interspecies hybrids has been revulsion, which has been expressed in the argument that such hybrids are unnatural. The Committee should not be misled by efforts to suggest that this is a minority reaction based on religious or pro-life views. It is undoubtedly the feeling of the vast majority of the population, even when the same individuals also argue strongly in favour of medical research. After 20 years of experience with GM food and other issues, policymakers should know better than to dismiss such views as 'irrational'. The point is that, in an inarticulate form, they express extremely valid concerns about science and the manipulation of nature. We should also bear in mind the important distinction between facilitating a natural process (as in IVF) and forcing nature to do something which it would never do naturally (as in cloning and creation of interspecies hybrids). Although it can be argued that all of modern medicine is unnatural, some things are more unnatural than others.

In view, public reactions about the unnaturalness of creating hybrid embryos is about two main concerns: (i) the lack of any respect for natural limits in the ideology of science, and (ii) the importance and meaning of species barriers.

4.1 Science and natural barriers

It is beyond the scope of this response to make general statements about science and the manipulation of nature, other than to emphasise that the current environmental crisis, and earlier events of the 20th century have surely demonstrated adequately that such concerns are very real. A naive equation of science and technology with progress will simply no longer do. In the present context, it is important to realise that the public's concerns about the unnaturalness of cloned interspecies hybrids is less about the question raised by conventional and academic ethics - 'is this right or wrong?' - as about the question, 'is this wise?'. The question about scientists' wisdom refers to science's inherent unwillingness to respect any natural limits or barriers and its determination to overcome them 'by any means necessary'. This can be seen at work in the present context: when scientists find that an unnatural technique (cloning) works very poorly, precisely because of its unnaturalness (cell differentiation in development normally works in one direction only because this is needed to create a predictable body plan for the organism), they seek to overcome this by brute force of numbers, by using animal eggs; but in doing so they add a further level of unnaturalness to the process (the species barrier), thereby increasing the odds against success. Is this intelligent or wise? We are not surprised that the public views this as a prime example of scientific lack of wisdom. Although philosophers like to dismiss the naturalistic fallacy in ethics, it would appear that the question of naturalness is, after all, relevant, at least to the question of whether particular scientific interventions are wise.

Concerning the existence of limits to scientific manipulations of nature, there is an important distinction between different types of interspecies hybrid. Scientists have assumed that it is enough to reassure the public that no monster will be born and that all they are doing is manipulating a few cells. But paradoxically, public concern about the proposed experiments is, in all probability, to some extent heightened rather than diminished by the fact that we are talking about the manipulation of embryos rather than animals or human beings. If we transplant animal tissue into a human being, the result will unquestionably be a human being. Manipulations at the level of organs or fully developed organisms (other than brain or reproductive organs) do not raise questions about the identity or species status of the resulting entity. However, manipulations at the subcellular level (as here), which can only be accomplished by intervening at the earliest stage of organismal development, can potentially result in much more profound changes in the resultant physiology and behaviour of the fully developed organisms, which do raise questions about the species status of the resulting entity. It is

the vulnerability of the embryo to such profound manipulation which excites concern, and raises valid questions about whether there should be a limit to scientists' manipulation of nature.

4.2 Species barriers and their meaning

Before discussing the reason for public revulsion at interspecies hybrids it is first necessary to clear away one piece of dead wood. It is true that interspecies hybridisation does occur in nature. However, it only happens between closely related species and the offspring are generally infertile. These are merely exceptions which prove the general rule that the biological utility of speciation is the creation of separate gene pools. Hybridisation across orders and at the subcellular level is completely unnatural.

In order to understand public revulsion, it is necessary to explore a fundamental difference in philosophical worldview between scientists and ordinary people. According to the materialist and molecular reductionist worldview of scientists, biological nature is composed of several types of complex macro molecules, which are composed of strings of small molecules common to all species. The only difference between species derives from minor differences in the ordering of small molecules within the long chains. In principle, for example, the difference between mitochondria from cattle and humans could be completely described by compiling a catalogue of the sequence differences in the genes that code for mitochondrial proteins etc.

This worldview does not admit of the idea of qualitative breaks in nature: nature looks rather like a well-blended soup. Within this paradigm, species differences are a matter of drawing an arbitrary line, and are to some degree illusory and unreal, a matter of quantitative not qualitative differences. This worldview is clearly apparent in the statements that stem cells derived from hybrid embryos are '99% human, 0.5% animal, or even that, rounding up, they are simply 'human'. Like genetic engineering, the mixing of human DNA and animal eggs is unproblematic in this view, because the two are not 'really' different in kind.

The ordinary person's worldview, which focuses on organisms rather than molecules is quite different. In this view, species are very definitely distinct, integrated wholes, different 'kinds'. Their characteristics are quite different and are what define the species: leopards have spots, zebras have stripes. Children's stories and folktales are preoccupied with these differences and their origin. We are not experts in anthropology, and we recommend that the Committee call anthropologists as witnesses; however we would conjecture that species differences are crucial in constructing a view of nature and of the world as composed of qualitatively different entities. Although apples and pears are closely related species, it is proverbially impossible to substitute one for the other, because they are qualitatively different. It may be further conjectured that the human psyche has a need for clear categories and for putting different items into separate pigeon holes.

The basis of revulsion, and of taboos is the inadmissible mixing of things that are different and should be kept apart, and the creation of entities that do not fit neatly into existing categories. In this view, hybrid animals, such as a pig with a head of a chicken, which cannot be clearly put in one box or the other are monsters, not merely because of their hideousness (which is merely an aesthetic expression of a lack of wholeness), but because they are not integrated wholes. A something-in-between has no place in the world. Such feelings are obviously heightened when one of the hybrid species is human, since additional issues of identity, legal rights and psychological issues come into play.

There is no doubt that the scientific materialist worldview is correct, at one level. However, where it fails is in providing any satisfactory account of how assemblages of very similar molecules come to produce species as obviously different as rabbits, cows and humans. There is as yet no good theory of the generation of 'emergent properties' in complex biological systems.

An emergent property of very complex systems that emerge through long processes of evolution is an integrity and internal harmony and a rigidity to manipulation that we might call wholeness. Even natural selection

cannot produce arbitrary concatenations of physiological characteristics that we see in fanciful or mythical hybrids: there is more than one physiological reason why pigs do not fly. In the same way, as we noted in section 1, it is asking a very great deal for subcellular interspecies hybrids to work. It is not necessary to invoke mystical or Aristotelian concepts of 'telos' to recognise that the wholeness and qualitative difference in embodied in different species is real and cannot be wisely or profitably tampered with, willy-nilly. Yet in contrast to evolution's slow process of elimination of that which does not work well together, scientists persist with trying to use the crude tools at their disposal to bodge something together in a hurry. They should not be surprised that these efforts are regarded with derision and revulsion by the public.

The wholes (species) that evolution produces do have to be regarded as qualitatively distinct, and the barriers between them need to be respected. It seems that the commonsense view of nature is, at the organism and species level, not only a better description than the molecular reductionist view, but is based on necessities of physiology and ecology that we might call, 'the wisdom of nature'.

Summary of section 4

Expressions of revulsion, and unnaturalness, are based on legitimate concerns about science and its unwillingness to set limits on manipulations of nature. Such views are not dependent upon particular religious convictions and have no lobby groups to represent them, as do scientists and patients, which is partly why we have been at such pains to explain them. The problem is not so much public misunderstanding as scientists' misunderstanding of the public. Scientists' inability to understand revulsion at breaching species barriers is based on a difference of fundamental worldview. Both worldviews have their merits: what is needed is mutual understanding, not dismissals of the public as irrational.

5. Conclusion

Human Genetics Alert supports the Government's decision to ban such research. In our view, it is unethical and of extremely little scientific value. The strong public opposition to such research cannot be dismissed as due to misunderstanding or 'irrationality', as if scientists had some monopoly on rationality. It is based on serious concerns, about science and its lack of respect for natural limits. Instead of lecturing the public on its irrationality, scientists would do better to critically reexamine their own worldview, and their often emotional and knee-jerk reactions to the idea of curbs on research.

In our view the Government should not insert the power to make regulations to overturn the ban into the Act. As with the genetic engineering of human embryos, it is important that any decision to reverse the ban should receive full parliamentary scrutiny, and the possibility to amend the text, which is afforded by debate on primary legislation, but not when changing regulations.

We believe that the decision to ban such research would have a positive effect on UK stem cell research, by not diverting research funding and the effort of top scientists into research will have little value.