Cambridge, December 2008

Science and Ethics of Cybrids

Dr Chris Willmott
Dept of Biochemistry
University of Leicester
cjrw2@le.ac.uk

University *of* Leicester

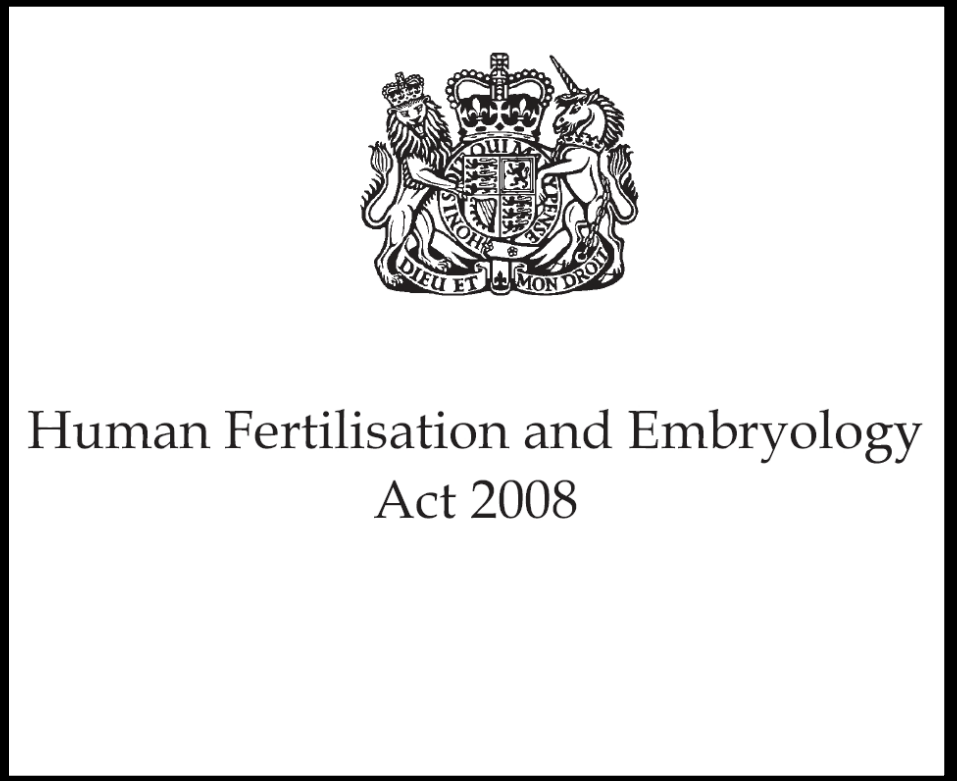
THE University of the Year 2008

Context for discussion

On 13th November 2008, Royal Assent was given to the Human Fertilisation and Embryology Act 2008

The new Act develops and updates legislation from the original 1990 HFE Act, including issues relating to embryo research, saviour siblings and parenting.

The new Act comes into force in October 2009 (the parenting aspects in April)



Getting the terminology right

Terms ‘chimera’, ‘hybrid’, ‘cybrid’, ‘interspecies embryo’ and ‘admixed embryo’ have been used in the media in connection with the HFE Act 2008

It is important to clarify the meaning of these different terms

What is a chimera?

From mythology

Homer's chimera

Minotaur

What is a chimera?

From science an organism composed of two or more different populations of genetically distinct cells originating in different zygotes

e.g. Goat embryo + Sheep embryo = Geep

Geep

What is a hybrid?

Offspring resulting from fertilisation of the egg from one species with the sperm from another species

Unlike a chimera, all the cells in a hybrid have the same genetic make-up, a combination to which both parents contributed, e.g.

Zebra x Horse = Zorse

Female Horse x Male Donkey = Mule

Male Horse x Female Donkey = Hinny

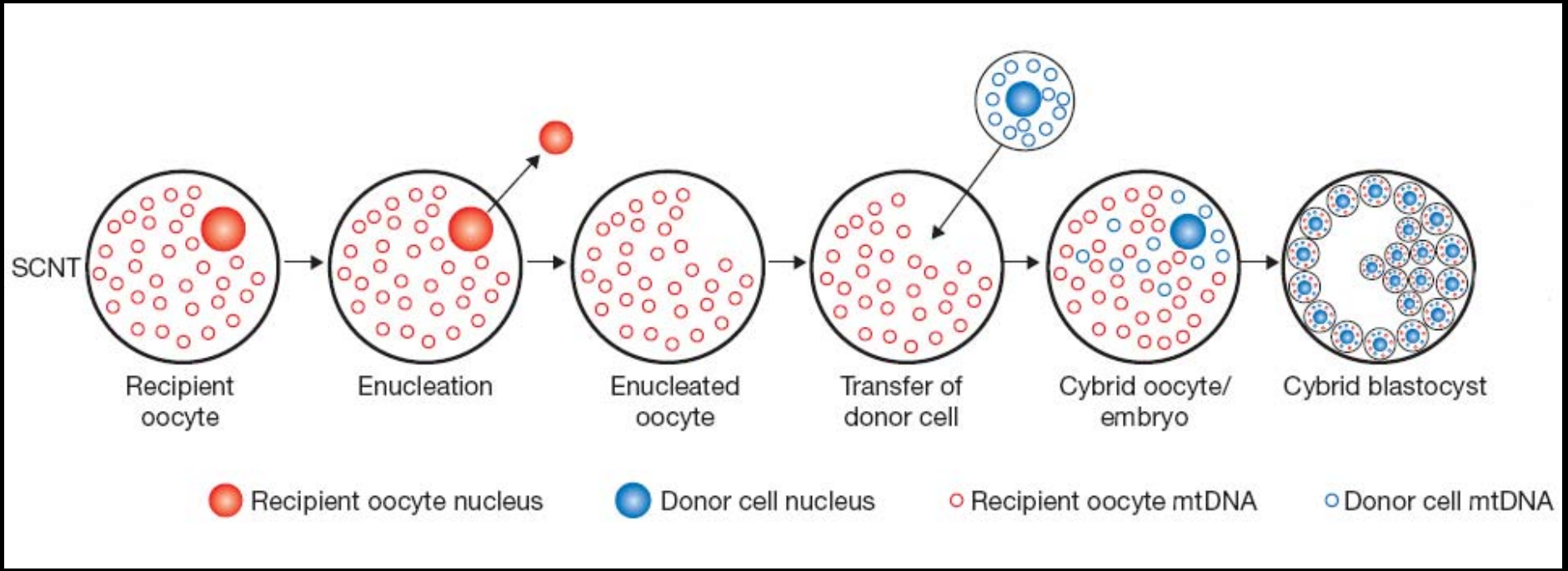
What is a cybrid?

‘Cybrid’ = cytoplasmic hybrid

Term first used in 1974 by Bunn *et al* working on mitochondrial DNA (mtDNA)

Current method involves SCNT (somatic cell nuclear transfer) as used to produce Dolly the Sheep

Creating cybrids by SCNT



Not ‘hybrid’ – no nuclear DNA from donated egg

Not ‘chimera’ – all cells of one type, not distinct

Nature Cell Biology 9:988-992 (2007)

What are 'admixed embryos'?

In early stages Bill referred to 'interspecies embryos' later change to 'admixed embryos'. Four classes of part human – part animal embryos included in Act:

Cytoplasmic hybrids (Cybrids): as above

True hybrids: human egg fertilised by animal sperm or vice versa

Human transgenic embryos: animal DNA introduced into one or more cells of human embryo

Human-animal chimeras: human embryo into which one or more non-human cells inserted

Plus 'catch-all' clause

Why make cybrids? (1)

Stem cells have great potential for regenerative medicine

Embryonic stem cells have greatest flexibility to become other sorts of cells

Human embryos are in short supply come from: IVF clinics (from older mothers) or from PGD (genetic abnormality likely and/or is of inadequate quality to implant)

Where else can embryos for research be obtained?

Why make cybrids? (2)

Younger women could be encouraged to make altruistic donation of eggs, or for payment

There are health issues associated with drug treatments to stimulate hyperovulation

Supplies would still be very limited

Animal eggs are readily available (e.g. at the abattoir)

Conclusion: taking animal oocyte and replacing nucleus with human nucleus would solve this shortfall

Arguments in favour

Under terms by which Human Fertilisation and Embryology Authority was established, The HFEA can only license an activity if it appears “necessary or desirable for the purpose of providing treatment services”

HFEA actually granted some permissions to do this work prior to new Act, arguing it was justifiable under original 1990 Act

Last Updated: Thursday, 17 January 2008, 12:09 GMT

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Green light for hybrid research

Regulators in the UK have given scientists the green light to create human-animal embryos for research.

The Human Fertilisation and Embryology Authority granted permission after a consultation showed the public were "at ease" with the idea.

Hybrids are made using an animal egg mixed with human genes

Experts said it was vital for research into life-threatening diseases.

Two centres, King's College London and Newcastle University, will now be able to begin their work under one-year research licences.

Arguments in favour

(1) Cybrid research will lead to new clinical therapies

[this work could lead to] “Major breakthroughs in treatments for Alzheimer’s, Parkinson’s and other serious diseases” Tony Calland (BMA)

“Medical researchers now believe that stem cell therapy has the potential to change dramatically the treatment of many other human afflictions” Gordon Brown PM

Current Biology 18:R356; BBC *‘Human-animal’ embryo green light*; BBC *In full: Gordon Brown embryo letter*

Arguments in favour

(2) Cybrid research will boost our understanding of how cells work

"Finding better ways to make human embryonic stem cells is the long-term objective of our work and understanding reprogramming is central to this."

Lyle Armstrong (University of Newcastle)

BBC *'Human-animal' embryo green light*

Arguments against

(1) Biologically, cybrids will not work

Permission to try does not mean something is achievable. Several biological problems to be overcome, including:

- Impairment in embryonic genome activation (EGA)
- Mitochondria problem

Mitochondria problem

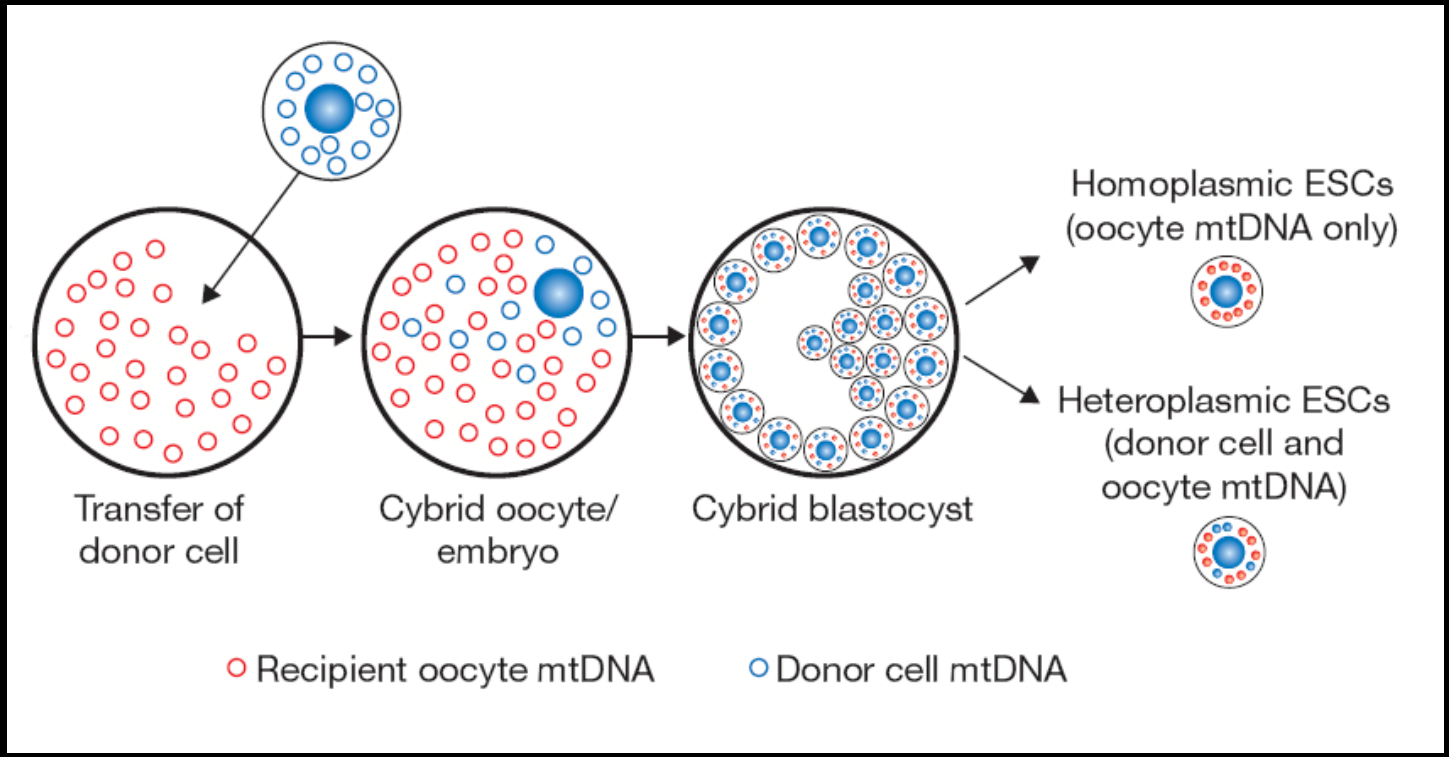
Mitochondria in oocyte = animal origin

Mitochondria have small number of own genes:

13 proteins for oxidative phosphorylation
22 tRNAs
2 rRNAs

Nuclear-cytoplasmic conflict: will components encoded by human nuclear DNA work with products of mtDNA genes?

Mitochondria problem



If fuse human cell will bring some mitochondria

Will any human mitochondria transferred be eliminated, be maintained or become predominant?

Nature Cell Biology 9:988-992 (2007)

Mitochondria problem – evidence?

Some success with interspecies experiments

1997-98 viable xenomitochondrial cell lines when chimpanzee or gorilla mtDNA transferred to human osteosarcoma nDNA cell, but not orangutan mtDNA

Several other reports using interspecies SCNT - success influenced by species relatedness?

Cells after iSCNT = sick?

Donor cell's mitochondria selectively eliminated?

Cybrids created

Mitochondria problem – evidence?

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Several other report
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Cells after iSCNT = s

Donor cell's mitocho

Cybrids created
Not ESCs yet

Page last updated at 17:04 GMT, Tuesday, 1 April 2008 18:04 UK

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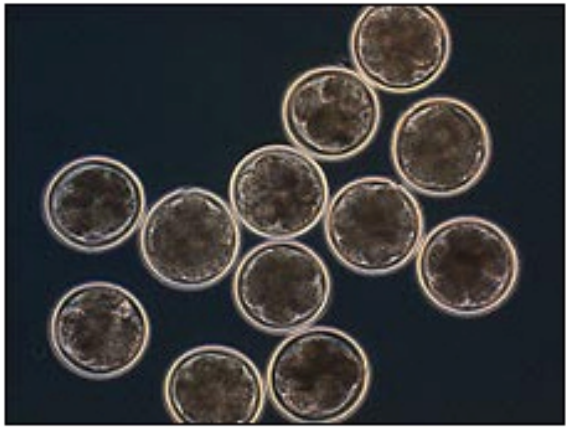
UK's first hybrid embryos created

By Fergus Walsh
Medical correspondent, BBC News

Scientists at Newcastle University have created part-human, part-animal hybrid embryos for the first time in the UK, the BBC can reveal.

The embryos survived for up to three days and are part of medical research into a range of illnesses.

It comes a month before MPs are to debate the future of such research.



They may look like any three-day-old embryos, but in fact these are hybrids

The Catholic Church describes it as "monstrous". But medical bodies and patient groups say such research is vital for our understanding of disease.

Arguments against

(2) Cybrids won't lead to clinical therapies

Even is ESCs are generated from cybrids they will be of no clinical use

Risk of infection

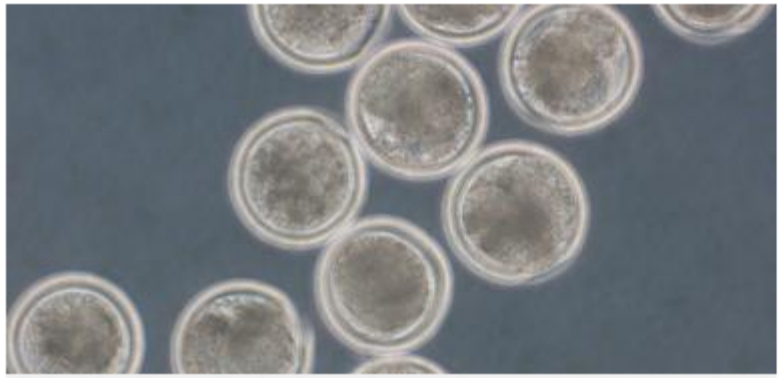
At best cybrids will be a research tool

Arguments against

From The Times

May 20, 2008

Cells from 'cytoplasmic hybrids' won't make it into humans



The outcome of the vote, however, is still a watershed for British science

Mark Henderson, Science Editor

Parliament's decision to approve research using "admixed embryos" that contain human and animal material is not going to lead to immediate medical breakthroughs.

Cells taken from "cytoplasmic hybrids" or "cybrids" - the main type of admixed embryos - are never likely to be transplanted into sick patients. Any insights that they might offer into diseases such as Parkinson's and Alzheimer's, too, are probably years away.

The outcome of last night's vote, however, is still a watershed for British science. First, it clears the way for experiments that could advance understanding of several devastating conditions, and the prospects of using all types of stem cell, embryonic and adult, in therapies.

Just as importantly, it confirms the value placed on free scientific inquiry in Britain, where regulation rather than prohibition is deemed the proper approach to ethically contentious research.

bies

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Arguments against

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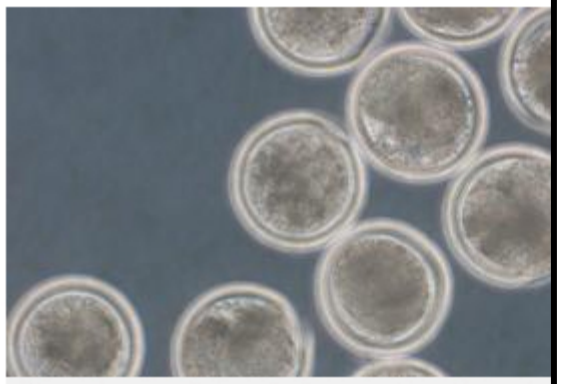

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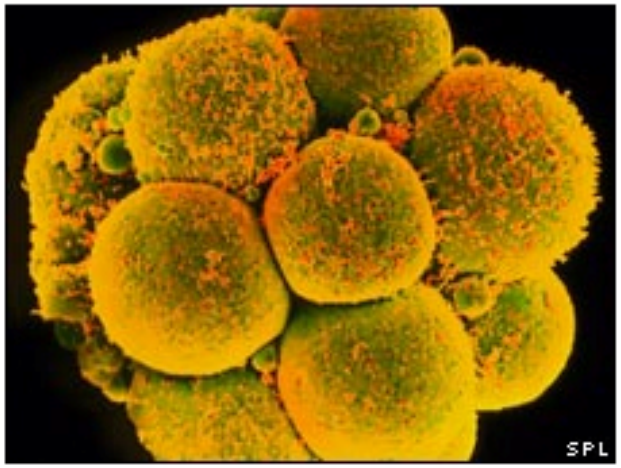
MPs back hybrid embryo research

The government has survived two big challenges to its controversial plans to change the law on embryo research for the first time in 20 years.



Critics say tinkering with human embryos is 'immoral'

A cross-party attempt to ban hybrid human animal embryos was defeated on a free vote, by 336 to 176.

Catholic cabinet ministers Ruth Kelly, Des Browne and Paul Murphy voted for a ban. PM Gordon Brown and Tory leader David Cameron both opposed it.

A bid to ban "saviour siblings" was voted down by 342 votes to 163.

Arguments against

(3) Repugnance: “Yuk factor”

“Most reasonable people would say that when you combine an animal and human embryo it is, by definition, monstrous” Claire Curtis-Thomas MP

“It does seem a little abhorrent at first analysis, but you have to understand we are using very, very little information from the cow in order to do this reprogramming” Lyle Armstrong (Newcastle University)

BMJ 336:1089 (2008); BBC News ‘Human-animal’ embryo green light

Ethical arguments against

(4) Making cybrids = Creating monsters

Catholic church (in particular) made much of arguments based on Frankenstein scenarios

The Young Family Patricia Piccinini

www.patriciapiccinini.net

Ethical arguments against

(4) Making cybrids = Creating monsters

Catholic church (in particular) made much of arguments based on Frankenstein scenarios

But: - nuclear DNA in cybrids all human

- embryos must be destroyed before 14 days
- absolute ban on implantation into woman or animal

However...

Opening the door?

“This is a momentous piece of legislation, which may bear directly, in the future, on the direction and perhaps even existence of humanity...”

Julian Savulescu

The new law on admixed embryos and the genetic heritage of the living kingdom. www.practicalethicsnews.com May 21st 2008

Opening the door?

"... it allows scientists to utilise the genetic heritage of the entire living kingdom on earth. Humans could benefit from the genes of any living or even deceased plant or animal. This might enable research to occur which could provide humans with the power to photosynthesise, to have sonar of a bat, the visual acuity of a hawk, the hearing of a dog or the balance of a cat"

Julian Savulescu

The new law on admixed embryos and the genetic heritage of the living kingdom. www.practicalethicsnews.com May 21st 2008

Opening the door?

"... it opens the door to transferring the building blocks of life, function, capacity, behaviour from other species into humans. Natural evolution would never have achieved this."

Prof Julian Savulescu
Uehiro Prof of Practical Ethics
Oxford University

The new law on admixed embryos and the genetic heritage of the living kingdom. www.practicalethicsnews.com May 21st 2008

Ethical arguments against

(5) Cybrid research blurs species boundaries

There may be some truth in this, but mixing of human and animal cells has occurred for many years

- animal heart valves?
- xenotransplantation?
- Rosie the cow (1997): human α-lactalbumin
- transgenic pigs, e.g. Factor VIII
- cell fusions in monoclonal antibody research
- teratoma testing: pluripotent cells in nude mice
- hamster test for sperm viability
- iSCNT human to rabbit/cow already done

Ethical arguments against

(6) Research violates human dignity

Arguments based on dignity are harder to pin down.

"Dignity is a useless concept" Ruth Macklin represent mainstream view of English-speaking bioethicists.

Other ethical traditions not so readily dismissive.
Fits with – but not exclusively with – Judaeo-Christian worldview. Given greater prominence throughout Europe.

BMJ 327:1419-1420 (2003)

Human dignity

e.g. Jacob Rendtorff identifies seven dimensions to the inviolability of individual human life, including:

- Every human must be considered as being without a price and unable to be commercialised
- The intrinsic value of a human being in a community or society

Human dignity is a central concept in UNESCO's 2005 *Universal Declaration on Bioethics and Human Rights*

Medicine, Health Care and Philosophy 5:235-244 (2002); http://portal.unesco.org

Ethical arguments against

(7) If we are uncertain, we ought not to do this

Easily lampooned = “Luddites and moralists” Alok Jha

Precautionary principle

Guardian blog “Comment is free”

Additional concerns about new Act

(1) Cybrids are not only permitted development

Range of admixed embryos – true hybrids, chimeras and transgenic human embryos - permitted under HFE Act 2008

More controversial, little debate

BMJ 327:1419-1420 (2003)

Additional concerns about new Act

(2) Presumed consent for cybrid production

Added between second and third reading, without public consultation.

"We also hope that the new legislation will be revised to allow researchers access to banks of well-characterized tissues and cells that were donated for research but not explicitly for the production of embryonic stem cells by somatic-cell nuclear transfer and other techniques" Justin St John *et al* (2008)

Nature 451:627 (2008)

Concluding remarks

To a first approximation debate boiled down to:

Utilitarian arguments in favour	Deontological arguments against

In current climate utilitarian argument dominate

"It is the role of legislators to be consequentialists"

Mary Warnock

New Statesman (10th February 2008)

Concluding remarks

Concern that on basis of utilitarian principles alone science will go without the necessary checks and balances

Science at best is not wisdom, it is knowledge. Wisdom is knowledge tempered by judgment.

Lord Ritchie-Calder

Activities for teaching about cybrids

Some suggestions for discussion starters:

1. Ask students to critique a published article on cybrids, e.g. *Law should recognize value of interspecies embryos*, letter to Nature by St John *et al* **451**:627 (7th February 2008)

2. Watch and critique 15 min section on cybrids from The Big Questions (BBC1, 9th September 2007, TRILT code: 0008D257)

3. Use an online BBC clip e.g. first 8 minutes of http://news.bbc.co.uk/1/hi/programmes/bbc_parliament/7410489.stm