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Code proposed for use of human tissue

A code of conduct for the banking and use of human tissue has been proposed by a group in the Netherlands. They say such a code needs to be internationally accepted to allow the development of supranational networks of tumour collections accessible via virtual tumour banks. The current lack of code may lead to the introduction of strict laws on tissue banking which "will slow the progress of cancer research, and, in the long term, will harm patients rather than protect them", they warn (*Nature Reviews: Cancer* 2003; **3:** 73–77).

The authors are part of a multidisciplinary group including patient representatives, lawyers, researchers and clinicians. It has been developing the "Code for Proper Secondary Use of Human Tissue in the Netherlands" for the past 3 years. The code is now binding for all members of medical and biomedical research societies in the Netherlands. The societies have been encouraged to inform their European counterparts about the code and the group hopes that it will be adopted elsewhere.

"IN THE UK WE ARE SHOOTING OURSELVES IN THE FOOT"

Strict laws, such as those that exist in Sweden, require patients to consent to storage of their tissue and provide separate consent for each individual research protocol which would involve it. At the other extreme, some European countries have no consent procedures at all. The Netherlands code is intended to occupy the middle ground.

It is based on the principle of allowing patients who object to opt out. Studies on directly identifiable tissue—where the researcher can easily find out the identity of the donor—still require written informed consent for each specific research use. However, where samples are indirectly identifiable or anonymous, as long as patients have been informed that their tissue could be stored for use in future research, and given the opportunity to opt out, their consent is implied.

The code applies particularly to existing samples in tumour banks held throughout the world. Many patients will not have been properly informed about what could be done with the tissue. Where re-examination of tissue has a direct impact on patient care, for example, a search for new biomarkers for cancer, consent can be assumed. The code applies where research is more esoteric.

"EVERYONE AGREED ON 80–90% OF THE ISSUES"

Dr Jan Willem Coebergh (Erasmus University, Rotterdam, The Netherlands), an *EJC* Editor, is co-author of the *Nature* report. "The issue is fraught with misunderstandings and misjudgements. One of the good things about developing a code is that when we defined the issues and problems, we found everyone could agree on 80–90%, and then we had to find a way through the rest. In Holland we were threatened with rather strict legislation, but since we developed the Code it has been put on hold. We will be self-regulating, which is much better than if we had waited until the law was introduced, and then had to object."

The legal situation varies elsewhere in Europe. In the UK, the so-called Alder Hey scandal, in which children's organs collected at post-mortem were stored without parents' consent, caused a national outcry. Its legacy has been a tightening of regulations which, according to Professor Peter Furness (Leicester General Hospital, UK), advisor to the Royal College of Pathologists, is causing enormous problems to researchers.

Until 1995, patients who had consented to surgery were considered to have consented to use of their tissues, unless they specifically objected. However current guidelines from the UK Medical Research Council and Department of Health require any research project involving stored tissue to be cleared by local ethics committees. The guidelines suggest that consent should be obtained "where practicable".

"The interpretation of this is very variable. A lot of ethics committees take it as meaning you can't do anything without signed consent. An awful lot of research projects have been blocked as a result," said Professor Furness. He said that renewed guidance, due out soon, leaves in the suggestion that consent should be obtained where it is practical to do so.

Professor Furness said he knows of two international studies in which the UK arm has collapsed because of the consent problem. "It went ahead in all other countries. We really are shooting ourselves in the foot as far as research is concerned in this country," he said.

At Peterborough General Hospital, UK, pathologist Dr Chris Wolmack said patients are generally happy for their tissue samples to be used. In a study presented to the CNIO meeting (Madrid, December, 2002), nurses

(continued overleaf)

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Tamoxifen "can prevent breast cancer"

Tamoxifen 'clearly' reduces the risk of oestrogen receptor (ER) positive breast cancer, according to an overview of the chemoprevention trials (*Lancet* 2003: **361:** 296–300). However, the drug has so far had no effect on all-cause mortality and the authors conclude that, except possibly in women at very high risk with a low risk of side effects, "tamoxifen cannot yet be recommended as a preventive agent".

The overview included all five randomised prevention trials comparing tamoxifen or raloxifene with placebo. It also used data from an overview of adjuvant trials of tamoxifen versus control.

Overall, the tamoxifen prevention trials found that it reduced ER-positive cancers by 48%, but had no effect on ER-negative cancers. Tamoxifen more than doubled rates of endometrial cancer, but no increase has been seen so far with raloxifene. Both drugs increased venous thromboembolic events.

Further steps that could reduce the side effects of tamoxifen include use of a lower dose, concomitant use of low-dose aspirin, and careful selection of women to exclude those with risk factors for thromboembolism and endometrial cancer. Alternatively, the authors say, "new agents such as aromatase inhibitors, which do not have these side effects and have shown early promise in preventing contralateral tumours, need to be investigated."

"ALL TRIALS MUST BE FOLLOWED TO THEIR CONCLUSION"

Deaths among the women in the trials are so far mostly from causes other than breast cancer, and the ultimate effects on breast cancer deaths cannot be judged except by modelling. The tamoxifen groups have a greater proportion of ER-negative cancers which suggests that case-fatality may be higher in the cancers that do arise in this group, the authors say.

Professor Jack Cuzick (Cancer Research UK, London) led the analysis and said the overview combined data on more than 40,000 women. "It is clear to us now that the drug can reduce the chance of high-risk women developing the disease," he said. "However, it is crucial that we follow all the trials to their conclusions and find ways to reduce the side-effects of tamoxifen before we can recommend that high-risk women take the drug to prevent breast cancer."

"The early data on raloxifene looks very promising: the trial shows that the drug can reduce the risk of breast cancer by 64% and cause fewer side-effects than tamoxifen. We will be awaiting the results of its direct comparison with tamoxifen in the American STAR trial with great interest."

"The future challenges for prevention research are to find ways to reduce the side effects of tamoxifen and investigate new agents such as aromatase inhibitors."

Carcinogenic herbal remedies

Herbal remedies such as European birthwort, which contain plants of the genus Aristolochia, are carcinogenic to humans, according to a report from the International Agency for Research on Cancer (IARC), Lyons, France. The IARC report found that cases of rapidly progressing kidney failure, tumours of the renal pelvis, ureter and urinary bladder were caused by mixtures of aristolochic acids in Oriental herbs.

"These herbal produces are marketed for uses, for example weight loss regimens, that were never contemplated in the traditional healing systems from which they emerged. The toxic properties of these preparations are in most cases not well known, and in many countries that import these products herbal medicines are not subject to rigorous standards with respect to manufacturing, efficacy, quality and safety," according to a statement from IARC.

The pyrrolizidine alkaloid riddelline is found in *Senecio riddellii* and other Senecio species, including *S. longilobus*, which is used as a herbal tea. It is clearly carcinogenic in rodents and classified as "possibly carcinogenic" to humans in the report. Similarly classified are anthraquinone derivatives, which are widely used as laxatives. They induce tumours in rats.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 82 "Some Traditional Herbal Medicines, some Mycotoxins, Naphthalene and Styrene is available from IARC Press. Contact press@ iarc.fr"

Proposed code (*continued*)

interviewed patients pre-operatively and asked for consent for surplus tissue to be stored and used by biomedical companies. The rate of consent was 98.8%, even though the tissues were to be used solely for commercial purposes. "It is uncommon to get an adverse comment. Patients are positive about what we are trying to do, especially where passing their tissue on could lead to a potential advance in diagnostics or therapeutics in their disease."

Dr Coebergh says this does not lessen the urgency of dealing with the legal and ethical issues. "Patients may be happy for us to use their tissues, but this doesn't count in law. There are higher things at stake. The law and the rule makers have to protect patients who may not completely understand or could be manipulated. And with the new sciences of genetics and proteomics, we will have so much detail about human biology. We need a way of dealing with this new situation."

The "Code for Proper Secondary Use of Human Tissue in the Netherlands" can be viewed in Dutch or English at www.fmwv.nl

EUROFILE

The Future of Stem Cell Research in Europe

After much dispute and many attempts at compromise, the European Council of Ministers approved the 6th Research Framework Programme (FP6) on 30 September, 2002. Their approval included an unexpected one-year moratorium on funding for embryonic stem cell research.

In a report due to be published in the spring, the European Commission is expected to recommend limited therapeutic use of cloned stem cells.

"A POLICY IS EXPECTED TO BE AGREED BEFORE THE END OF 2003'

However, the Commission report is also likely to recommend that Member States have the final say on whether any kind of stem cell research, including EU-funded projects, will be allowed in their countries.

If this is the case, and if the European Parliament is happy with the report, it will end a lengthy chapter of accusations of undue pressure and threatening behaviour, which has exercised many MEPs and Commission officials over the past two years.

The Council—the central decision-making body of the EU—and the Parliament had reached an agreement in June 2002 which permitted EU funding of embryonic stem cell research in Member States where it was allowed. However, this agreement was not in writing, and the Council, at its meeting in July, adopted the one-year moratorium instead. Italy was the only country to oppose the proposal, which came from the Danish Presidency of the EU.

The agreement caused uproar among some members of the Industry, External Trade, Research and Energy Committee, which takes the lead on discussions of EU research programmes. The chairman, Carlos Westendorp y Cabeza, MEP, expressed heavy criticism of the Danish Presidency and claimed that Parliament would block the entire budget for research if the moratorium went ahead without consultation.

Dr Peter Liese, a German Christian Democrat MEP and former rapporteur of the Parliament's working party on bioethics and biotechnology said: "This threat is absurd. The Parliament lost its possibility to determine these rules when adopting the Research Framework Programme without any clearly defined rules on this topic. The Council of Ministers is completely free to determine rules for research on embryos and embryonic stem cells."

The threat prompted further negotiations and eventually it was agreed that a new proposal on stem cell research, based on an in-depth technical, ethical, and political study, would be presented by the Commission to the Parliament for consultation. A policy is expected to be agreed

"ONLY 9 OF 15 000 RESEARCH PROPOSALS CONCERNED STEM CELLS"

before the end of 2003. Until then, there is agreement that "the Commission will not proposed to finance such research projects, unless they involve already established banked or isolated human embryonic stem cells in culture."

Ethical issues have always been a thorny problem on the EU stage, but this one seems to have been particularly difficult partly because of the complicated nature of stem cell research. Research Commissioner Busquin, most of the members of the Industry and Research Committee, and a majority of the Member States represented in the Council felt it was not possible to create defined ethical limits for this research.

However, some feel that a sledgehammer is being used to crack a nut. "It is worth looking at the figures that Busquin has mentioned", says Peter Liese. "The Commission was said to have received 15,000 expressions of interest in FP6. But the proposals concerning human stem cells research focus on adult and umbilical cord stem cells. Only nine are concerned with embryonic stem cells. Why couldn't he simply have said that he would not consider those nine proposals? That would have been the solution to a big problem."

Recent claims by the Raelian sect that cloned babies have been born in the US and Europe are likely to inflame the debate further. Commissioner Busquin has already affirmed his opposition to reproductive cloning and his support for the Franco-German initiative for a world convention banning the reproductive cloning of human beings. "Reproductive cloning of human beings must be condemned, not only on obvious ethical grounds and on the basis of common human values, but also because it is an entirely irresponsible practice from the scientific point of view: experience with animals has shown that cloning involves a huge number of risks and uncertainties", he said in January.

Such cloning is already banned under FP6. Specifically outlawed are any research activity aimed at human reproductive cloning, at making permanent alternations to the human genetic heritage and making such changes hereditary, and at creating human embryos solely for research.

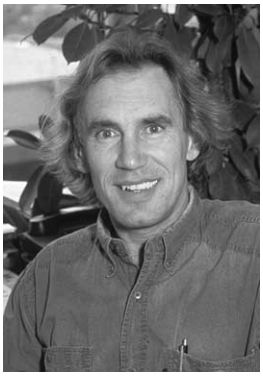
Commission spokesmen have denied that the report due to be published in the spring would tackle the issue of reproductive cloning, but recent events are bound to muddy the waters for all stem cell research. Whether, this time, reaching an agreement will be more complicated as a result remains to be seen. But just as stem cells seem to be showing promise in treating patients with advanced leukaemia and lymphoma, it would be a shame if the research became a political football, and a decision made on the basis of an instinctive reaction against something which has most likely not happened at all.

Mary Rice
Brussels

Pioneers in Transgenics win Award

The Charles Rodolphe Brupbacher Prize for Cancer Research, 2003, has been awarded jointly to Professor Erwin Wagner (Institute of Molecular Pathology, Vienna, Austria) and Professor Rudolf Jaenisch (Whitehead Institute of Biomedical Research, Cambridge, Massachusetts). The prize, awarded by the Swiss-based Charles Rodolphe Brupbacher Foundation, is awarded every other year. Recipients are selected by an advisory board of scientists, and will each receive 100,000 Swiss Francs.

Professor Wagner was chosen "for his contribution to our understanding of the role of oncogenes of the *fos* and *jun* family in development and in cancer"; Professor Jaenisch "for his contribution to our understanding of the role of epigenetic DNA modification, in particular cytosine methylation in genomic stability and cancer."

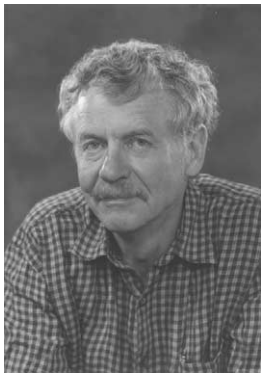


Professor Erwin Wagner

Over the past 15 years, Professor Wagner has analysed oncogene function in the intact mammalian organism, with particular emphasis on the transcription factor complex AP-1 (c-fos and c-jun), and signalling molecules such as the EGF-receptor. He discovered the EGF-receptor's role in the development of skin tumours and contributed to studies on growth control of endothelial cells.

Professor Wagner was always conscious that oncogenes do not exist for the purpose of bestowing cancer on us and sought to identify their physiological functions. He used transgenic and knockout mice to demonstrate that cancer and control of developmental pathways are two sides of the same coin. For example, in AP-1 function, he identified c-fos as a key regulator in bone development, and discovered the role played by c-jun and jun-phosphorylation in stress-induced apoptosis. His gene replacement and genetic complementation analyses demonstrated that JunB can act as a tumour suppression gene in mice.

"Erwin Wagner is not only a remarkably productive scientist, but also a gifted teacher who has been able to pass his scientific philosophy and his rigorous, intensely focused approach to biological problems on to his students and co-workers," the awards committee noted. "The transgenic models of abnormal differentiation and growth pioneered by Erwin Wagner have led to many insights into the biology of cancer. It is to be expected that the wealth of paradigms that he has created in the past years will pose new questions, and yield many additional answers, in time to come."



Professor Rudolf Jaenisch

In his early work, Dr Rudolf Jaenisch pioneered the use of transgenic mice as model systems of human malignancy. He showed that animals carrying a hypomorphic allele of the major cytosine DNA transferase, Dnmt1, were substantially less prone to acquiring intestinal polyps in a tumour-predisposing genetic background. It implied that cytosine methylation promotes the transformation of the intestinal epithelium.

More recently, he has demonstrated that DNA hypomethylation leads to genomic instability and thus also to cancer, predominantly lymphomas, which suggests that DNA methylation protects lymphocytes and other cells from transformation.

The awards committee stated, "Taken together, Dr Jaenisch's studies demonstrate that cytosine methylation plays different roles in the genesis of cancer. It is to be anticipated that the model systems developed in his laboratory over the years will substantially further our understanding of the tissue-specific transformation process and thus help in the development of more effective cancer treatment."

IVF link to retinoblastoma?

Children born as a result of in-vitro fertilisation may be at increased risk of retinoblastoma, say researchers from the Netherlands (*Lancet* 2003; **361**: 309–310). They note in a research letter that, between November 2000 and February 2002, they diagnosed retinoblastoma in 5 patients born after IVF.

Previous studies have suggested that IVF babies do not have a heightened risk of cancer. However, they calculated that if 1–5% of births in the Netherlands are as a result of IVF, the relative risk of retinoblastoma among these children is almost 5-fold. If 1% of births result from IVF, the relative risk is increased 7-fold. "This possible association of an increased risk of retinoblastoma in a population-based study needs to be established," they say.

A commentary on the paper (*Lancet* 2003; **361**: 273–274) points out that most mothers of children with malignancies do not volunteer information about undergoing IVF. If 3.0% or 3.5% of children born in the period studied were born as a result of IVF, the relative risks of retinoblastoma would be much lower than those recorded, it states.

"Whatever the 'true' incidence of retinoblastoma is after IVF, there is little doubt that a heightened awareness and a multidisciplinary approach with a closer follow-up of children conceived with assisted reproductive technologies are needed," it concludes.

PODIUM

Why economics matter

Professor Ralph Crott is head of the EORTC's Health Economics Unit. He trained in applied economics, technology assessment and clinical epidemiology, and worked on economic evaluation of drugs, before becoming Professor of Pharmacoeconomics at the University of Montreal. He is co-chairing the EORTC's 3rd European Conference on the Economics of Cancer (Brussels, 7–9 September 2003).

Professor Ralph Crott

How important are health economics?
Increases in health care expenses are generally growing faster than economic growth and state revenue. Even allowing for needed increases in health care budgets, there will always be a limit to financial and manpower resources as demand for health care is potentially infinite. Some choices will always have to be made.

Why are costs increasing so steeply?
New medical technology, including drugs and diagnostic equipment, is generally more expensive than old technology and is driving the growth of expenses along with greater demand by patients and an aging population. On the other hand, it leads to better medical care and improved clinical results.

How keen are health professionals to enter this debate?
There is a worldwide reluctance among healthcare professionals. As students, they are never taught about the structure or financing of the system in which they will be working. They face issues of cost every day of their working lives, but they have no preparation for it. The US and Canada are more cost conscious than elsewhere, partly because of how their healthcare systems are financed. Where closed budgets are introduced, such as in the UK, cost consciousness is raised because choices have to be made. Health professionals tend to be in general less cost-conscious in countries where they are paid on a fee-per-patient basis, with no budgetary constraints.

Who should conduct economic evaluations?
We need a combination of expertise in statistics, economics, clinical epidemiology and clinical medicine. In Europe, groups are mostly academic and run by economists; in the US and Canada the work is more often carried out in pharmacy schools or Schools of Public Health. There is an urgent need for integrated multidisciplinary teams working on defined projects in independent research organizations.

Medical assessment boards or groups tend to work from the perspective of the health system or insurers. The EORTC is exceptional in that it is a non-profit-making organisation, independent of government or industry with an international approach. There are few cooperative groups like this anywhere in the world.

How accurate are economic evaluations?
Ideally, you need a large database linking the health records of patients, initial hospital treatment received, toxicity, care received after discharge, including community care and re-hospitalisation, appointments with GPs and nurses, and the outcome of treatment.

In Europe, few databases like this exist and until we have this detailed data we will only have a partial picture. We need to know about the downstream effects of treatments in every day practice.

Are the issues in cancer different from those in other diseases?
The complexity of care with its interaction between disciplines makes follow-up difficult, but that is the same in other complex diseases like AIDS or diabetes.

Should economic evaluation be an integral part of clinical trials?
Clinical trials are not always the best way of assessing effectiveness. They may be too short or designed to look mainly at survival and disease progression. We are also concerned with other aspects of care like Quality of Life and follow-up and end-of-life care. Health economic evaluations need to answer requirements by health authorities for drug registration, but are also academic research on therapeutic approaches with registered compounds. A clinical trial tells you what happens in a controlled environment. But there is a need to check up on what happens afterwards, whether things that work in trials actually work in everyday clinical practice and to optimise everyday treatment strategies.

How transferable are economic assessments?
They need to be conducted locally. Every European country has a different health care system and different costs. Analysis of a procedure in Sweden could have a quite different outcome to one carried out in Germany. This is the attractiveness of an organization like the EORTC with its unique European focus.

What developments do you expect over the next 10 years?
Increasing momentum for evaluations to be carried out by 3rd parties. And, I hope, increasing involvement by clinicians. Not all, but some must engage in this process. In general, good medical care is good economics; optimal medical care is cost effective. Diagnostic or follow-up tests that don't alter medical practice are best avoided from both points of view.

What do you hope the conference in September will achieve?
It will bring together all health economists in the field of cancer, and be an exchange forum where we can learn from each other on methods and databases. There will be presentations on the advances in methodology over the past 3 to 4 years, and on links with clinical analyses. We're inviting a panel of officers from medical and drug assessment boards. Economic analyses are not being used sufficiently by policy decision-makers, often because committee members don't understand the statistics. This needs to be addressed.