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# Purity and the dangers of regenerative medicine: Regulatory innovation of human tissue-engineered technology

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## Abstract

This paper examines the development of innovation in human tissue technologies as a form of regenerative medicine, firstly by applying ‘pollution ideas’ to contemporary trends in its risk regulation and to the processes of regulatory policy formation, and secondly by analysing the classificatory processes deployed in regulatory policy. The analysis draws upon data from fieldwork and documentary materials with a focus on the UK and EU (2002–05) and explores four arenas: governance and regulatory policy; commercialisation and the market; ‘evidentiality’ manifest in evidence-based policy; and publics’ and technology users’ values and ethics. The analysis suggests that there is a trend toward ‘purification’ across these arenas, both material and socio-political. A common process of partitioning is found in stakeholders’ attempts to define a clear terrain, which the field of tissue-engineered technology might occupy. We conclude that pollution ideas and partitioning processes are useful in understanding regulatory ordering and innovation in the emerging technological zone of human tissue engineering.

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## Introduction

Pollution, uncleanness, contamination, taboo, exclusion, segregation, and partitioning represent fundamental axes for the normative classification and ordering of sociomedical and everyday life. The world of medical technology is becoming characterised by an increasingly complex, hybrid mixing of materials under the impetus of biotechnology.

These technologies, often involving manipulation of human tissues or cells, raise risks of physical ‘pollution’ and diseases of the human body, accompanied by risks to the body politic (Franklin & Lock, 2003; Brown & Webster, 2004). Technologies such as organ transplantation, stem cell therapy, xenotransplantation, and gene therapy raise questions of social values that impinge upon the political process of creating socially acceptable but innovation-friendly regulatory frameworks.

Tissue engineering (TE) is a set of biotechnology-driven therapies being promoted in many quarters as a part of regenerative medicine. It includes implants for knee cartilage repair, ‘living’ skin

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tissue for chronic ulcers and burns, and bone regeneration products. These are in the healthcare marketplace now (Bock, Ibarreta, & Rodriguez-Cerezo, 2003), and future developments may include vascular prostheses, organ-assist devices (liver, kidney), bio-engineered whole organs, complete body structures (heart valves, joints), and repair of neurological tissues. They are often conceived of as ‘borderline’ products, emphasising that they have not been catered for by the existing pan-European regulatory framework. Adoption of medical technologies has rested on appraisal of medicines and medical devices and biologics, classifications which have different regimes of assessment. There is a widely though not unanimously perceived need for ‘new regulation’ (Cox & Tinkler, 2000 for a regulators’ perspective).

The study of classification systems is fundamental to social science, and the advance of information systems, mass media, and complex socio-technical systems suggests that they are even more important in contemporary, global, interactive societies (Bowker & Leigh Star, 2000). At the same time, the transgressive nature of biotechnologies, and the increasing public concern about complex health risks such as BSE, suggest that a focus upon boundary-threatening ‘pollutions’ may also be rewarding. Anthropological analysis holds that concepts of pollution and purity are strongly related to the cultural ordering of societies (Douglas, 1966). Pollution ideas work instrumentally, for example by the socially powerful using ideas of contagion to uphold social rules, or they work as symbols: ‘Some pollutions are used as analogies for expressing a general view of the social order’ (1966, p. 14). Gabe (1995) has emphasised the importance of Douglas’ approach in focusing on why societies proscribe certain practices. The societal perception of contamination is frequently accompanied by a regulatory response in the form of quarantining or partitioning (Douglas: ‘pollution ritual’). We add here that the *material* consequences—disease, disability—of physical pollution are also important. Once dismissed as ‘medical materialism’, public health risks raised by biotechnology mean that the framing of material risks has become crucial to their social management. Pollution practices are thus matters both of public health and ordering social experience.

Douglas’ conceptualisation of pollution categories has been criticised as portraying socio-material categories as overly static (e.g., Brown &

Webster, 2004, p. 130). The subverting character of biotechnology suggests that socio-material boundaries have to be regarded as plastic. Rather than underpinning social order such categories are instead involved in processes of re-ordering societies’ institutions, cognitive domains and moralities. Society, material technology and biochemical processes interact to produce hybrid phenomena seen as uncertain and often dangerous, such as global warming and BSE. Medicine has become a key locus for such uneasy convergences, which challenge social meanings and regulatory powers. (We develop theoretical aspects of this discussion elsewhere—Brown, Faulkner, Kent, & Michael, 2006.)

Regulation may be *constitutive* of new technologies (Bud, 1995). We take up the term ‘regulatory order’ (Faulkner, Kent, Geesink, & FitzPatrick, 2004) to describe webs of interlinked laws, regulations, guidance, surveillance and more or less contested practices, which might ‘govern’ and construct technological fields. ‘Regulatory ordering’ designates processes in which a variety of actors may claim jurisdictional authority over commercial, public, cognitive, technological, or moral territories. ‘Technological zones’ (Barry, 2003), akin to the notion of ‘technoscapes’ (Appadurai, 1990), may be associated with ordering of regulatory jurisdictions, and may be aligned with political entities such as nations, empires, or trading blocs, or may be less identifiable with political geographies.

The sheer quantity of regulatory measures bearing upon TE technologies has been growing rapidly. Within the European Union an evolving collage of regulatory instruments are relevant. Details have been given elsewhere (Kent, Faulkner, Geesink, & FitzPatrick, 2006a) and are referenced as appropriate below. In the European Union, two main regulatory movements are most *directly* relevant for TE activity. These are embodied in the Directive on standards of quality and safety for the sourcing and processing of human tissues and cells (adopted by the European Parliament in 2004—we refer to this as the Tissues and Cells Directive or TCD henceforth (EC (European Commission) DG Enterprise, 2004); and a proposed Human Tissue-Engineered Products regulation (under the auspices of DG Enterprise; see EC DG Enterprise (2004)—we will refer to this as the Tissue Engineering Regulation or TER). The latter is still evolving at the time of writing and is drawn upon less in this paper. These movements focus respectively upon

tissue banking activities, and on the production and bringing-to-market of engineered products.

Here, therefore, we aim to understand the development of regenerative medicine via an approach attending to pollution practices and classificatory work in the policy domain, and we aim to show how these linked processes are part of the ordering of a TE zone. Our discussion runs on two tracks. Firstly, we hazard the application of notions of pollution and purity to healthcare policy innovation. We consider stakeholders' perceptions of 'pollutions' raised by these technologies and ask whether there is evidence of any systematic response. Secondly, in parallel and equally important, given risks of material and social pollutions, we seek to understand the classificatory discursive strategies that stakeholders employ in the shaping of a TE zone. We identify four arenas of socio-political activity and policy discourse, which are particularly salient in shaping the prospects for TE: firstly, the arena of governance and regulatory policy itself; secondly, industry, commercialisation, and the marketplace; thirdly, the 'evidentiality' manifest in public organisations' urge toward 'evidence-based' policy; and fourthly, the arena of publics' and technology users' values and ethics. Each arena is viewed as a site where different constellations of actors interact.

The paper now considers each of these four arenas of socio-political activity. The analysis draws upon data from fieldwork and documentary materials with a focus on the United Kingdom and European Union, gathered between 2002 and 2005. Many of our interviewee-informants occupied key positions in national regulatory bodies, the European Commission, as professional opinion-leaders, on advisory groups or committees and as industry and other stakeholder groups' representatives. We interviewed 63 people, mainly face-to-face, and collected a wide variety of policy-related documents including European Parliament debates, drafts of European regulations and associated 'public' consultation documents, position papers from EU-level trade associations, regulatory agency documents, and manufacturers' and professional codes of practice. Interviews were divided between the UK and Europe, and apart from the UK included organisations in 'Brussels', Sweden, Denmark, Belgium, Spain, Italy, the Netherlands, Germany, France, and Switzerland. We also observed a variety of scientific, industry, regulator, and policymaker discussion forums. Extracts from these data are presented in the discussion below.

### *Regulatory policy: grubby governance and risky tissues*

Regulatory policy for tissue-engineered technologies grapples with a number of diverse issues. Notable among these are the distinctiveness of TE activity in relation to other technological fields; the challenge of technologies that appear to be socially or morally dangerous; the perceived need for regulatory categorisations that render new technology regulatable and thus provide a pathway for producers to reach consumers; and complex inter-relationships between actors in contemporary technology governance networks.

Suggestive evidence of the increasing stringency of pollution-related regulatory activity in the UK is provided by a series of new policies in the form of voluntary codes produced by the Department of Health and the (then) Medical Devices Agency<sup>1</sup> in collaboration with industry and profession representatives. These policies are enshrined in guidance and codes of practice on microbiological safety of human organs and cells, (Department of Health, 2000), for tissue banks (Department of Health, 2001), and for 'Human-derived Therapeutic Products' (MDA (Medical Device Agency), 2002). The latter 'specifies the scientific principles underlying the production, quality assurance and safety assessment of products that use material of human origin'. It sets out the importance of a quality assurance system for organisations producing and supplying human tissue products drawing on existing standards for quality management, risk management and risk assessment. The code of practice on tissue banks tackles accreditation of tissue banks and safety of donations.

Innovation in tissue-engineered technologies affects the *material risks* of the technologies themselves. These are manifested for example in various forms of regulation such as the voluntary guidelines noted above and perceived needs, in clinical communities for example, for more searching assessment regimes. Response to the perceived material, technological risk is illustrated, from the clinical community, below.<sup>2</sup>

<sup>1</sup>Now the Medicines and Healthcare products Regulatory Agency (MHRA).

<sup>2</sup>The varieties of risk that scientists and manufacturers perceive in TE are explored elsewhere (Geesink, Faulkner, Kent, & FitzPatrick, forthcoming).

‘... tissue-engineering is facing considerable scepticism and anxiety... tissue engineering research is in its infancy and products of sufficient quality for routine clinical use remain a long way away. We anticipate that stringent testing of these products will be carried out before they are considered for human implantation’ (Jallali, 2003).

A second comment in the British Medical Journal referred to the SARS epidemic (severe acute respiratory syndrome), and expressed the growing movement to create strong preventive systems for partitioning and managing potential risks. This discourse draws upon high profile public fears:

‘In ex-vivo corneal stem cell expansion, the cells are grown in media containing various growth factors and co-culture with transformed mouse fibroblast cell before transplantation onto corneas with stem cell deficiency... Clearly, there is a need for accreditation of laboratories conducting such work. The use of...co-culture system must be in consultation with United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA). Without such stringency, there will be a risk of cross-animal contamination such as the one we witness (*sic*) recently in outbreaks of SARS virus’. (Kong, 2003)

UKXIRA is committed to extending the reach of its definition of xenotransplantation, to include the culture media in which products are manipulated (UKXIRA, 2003; Brown & Michael, 2004). Further testimony to the purificatory trend comes from our observations in a UK hospital meeting to discuss implementation of the TCD, in which the motif of the ‘few pieces of tissue kept in a fridge at the back of the consultant’s office’ was deployed as a recurring danger sign. In Europe, therefore, current initiatives reflect a growing sense of urgency about the need for new controls. A more recent instance is specification by expert groups of draft technical requirements related to the TCD (EC Health Consumer Protection Directorate-General, 2004, 2005). The latter for example declares: ‘There must be a documented system in place that ensures the identification of every tissue and/or cell unit at all stages of the activities for which accreditation... is sought’. These examples are clearly a sign of the increasing ‘regulatory reach’ (Welsh & Evans, 1999) of purification policies and their surveillance.

Having considered the regulatory response to growing perceptions of material pollutions associated with human tissues and engineering technologies, we now turn from ‘pollution ideas’ to the second track of our discussion, the strategies used by stakeholders in this arena. Our primary observation is that a strategy of what we will term ‘partitioning’ is evident. This attempted partitioning of cognate regulatable technologies as distinct from ‘tissues and cells’, and tissue-engineered products can be illustrated in a wide variety of discursive settings such as multi-stakeholder forums and European policy debates. A key aspect of the emergence of new regulation around TE products is debate about the *scope* of new regulations. This has taken the form of attention focused on what might be included or excluded in new legislative instruments. Commissioner Byrne, commenting in the European Parliament on the debate on the TCD made the following statement:

‘... it is not appropriate to include organs in the scope of this directive... their transplantation requires a different policy approach due to their specific nature... Following the example of the blood directive... *we would like to get the science right first, before tabling a legal instrument in this sensitive area.*’ (EC (European Commission), 2003). (author italics).

On the exclusion of other possible novel technologies:

‘... this is not the time to permit cloned human embryos or hybrid human animal embryos to have their cells and tissues used for transplants. The demise of Matilda, the Australian sheep which disintegrated, serves as an awful warning that this is a very young area of science and experiment...’ (MEP Bowis in EU, 2003) (Matilda was Australia’s first cloned sheep, produced using techniques similar to Dolly in Scotland).

‘Organs, tissues and cells of animal origin for human therapy...pose different regulatory problems that will need to be addressed in due course’ (from the Explanatory memorandum to the proposal for the TCD (EC DG Sanco, 2003)).

Both extracts point to the perceived need for caution and taking account of scientific uncertainty regarding these novel technologies, while the second extract argues for exclusion of xenotransplantation.

A similar partitioning process could be seen in the case of policy discourse around the proposed TER:

*‘Realpolitik* dictated the exclusion of stem cells—it would sink the legislation, over-complicate the legislation’ and in reference to xeno-transplantation, this was a ‘step too far at the moment’ (UK regulator at Europe-wide regulators/industry forum, fieldnote, 2003).

In fact this particular interpretation of the *realpolitik* turned out to be mistaken—the more recent proposals for consultation for a TER in 2005 do not exclude stem cell therapy in the sense conveyed here. Rather ‘somatic cell therapy’ is being construed under the medicinal regulatory regime as one of several types of ‘advanced therapy’ of which tissue-engineered technologies are another (EC DG Enterprise & Industry, 2005).

In summary, together with partitioning and boundary-setting strategies in the regulatory process, we have noted an increasing stringency in the standards and accountabilities of human tissue users, illustrated by the policy discourse and actions of a variety of regulatory actors. Together with regulatory policymakers, representatives of industry are the major stakeholders active in shaping TE regulation and it is to these that we now turn.

*Trade and commercialisation: dangerous traffic, messy markets*

A number of aspects of commercialisation may be understood by application of concepts of pollution and partitioning processes. These include the constructive, socio-political definition of TE as a technological field, technical standards, and competitiveness vis-à-vis different market areas. The increase in traffic in human tissues and cells is one of the framing assumptions for the increasing regulation being brought forward. On the one hand, the EC’s Directorate General Sanco is seeking to fulfill the requirement to protect public health, and has produced the TCD. The introductory remarks prefacing this directive state that ‘As tissue and cell therapy is a field in which an intensive worldwide exchange is taking place, it is desirable to have worldwide standards’.

It is important for commercial and regulatory interests that a clearly delineated ‘zone’ of activity can be identified. The constructive aspect of zone-building in the context of European industrial and governance networks has been explored recently

(Barry, 2003, p. 25). The definition of the contour lines of such zones is a matter of negotiation, in which national and sectoral interests may well play an important part.

The TCD was initially focused on the activities of procurement and processing of tissue within the tissue bank sector. However in the political debate that ensued the industry sector lobbied for a ‘level playing field’, which would allow them to procure tissues directly. As a consequence both not-for-profit and for-profit tissue establishments may be accredited. Moreover in order to overcome national differences regarding the inclusion of different cell types, the principle of subsidiarity was applied to allow member states to put in place additional restrictions on the use of specific types of cell.

The TER too is a site for contesting and negotiating the interests of different stakeholders among human tissue users. For example, there is tension between the interests of traditional tissue banking culture—largely associated with clinical and hospital practices within national healthcare systems—and the culture of trans-local, transnational technical standards in the commercial R&D sector.<sup>3</sup> This has consequences for the scope that particular regulatory instruments might have, and for the definition of the therapeutic and/or industrial zone:

‘traditional tissues will be excluded from new tissue engineering regulation for no good technical reason’ (EC Regulation consultant A-EU2, interview 2004).

and

‘... the new regulatory track with a separate office and people busy with this is one absolute necessity if Europe doesn’t want to be left in the dirt...’ (Clinician, CL-EU5, interview 2003).

The latter statement combines reference to a perceived need for regulatory specialisation with a comment about the competitive position of a European TE zone compared implicitly to the USA. Similar concerns are brought together in statements that discuss TE in relation to investment and show the polluting potential of, and desire to partition TE away from, stem cell therapy as a regulatable field:

<sup>3</sup>This phenomenon is discussed somewhat further in Kent, Faulkner, Geesink, and FitzPatrick, (2006b).

‘When you explain tissue engineering to people, everyone understands what it could do for mankind and...what it can do to the economics of a company that are successful..., you easily start things and the regulatory issues or the difficulties with stem cells are too high.... And there’s been hype definitely...’ (Scientist, S-EU2, interview 2003).

The partitioning response to perceived pollutions is also evident in debate about technical standards. Standardisation is a neglected topic in analysis of technological society and especially the building of technology zones (Barry, 2003). Representatives of the larger companies active in TE technology portray themselves as being in the vanguard of technical standards. A number of technical standards already apply to products containing human tissues or cells. According to this manufacturer involved in ‘regulatory affairs’:

‘Whereas going back to the example of your tissue bank, the surgeon can come along and say can you grow me up some of these cells, the tissue bank says yes of course...the surgeon implants them with no knowledge of that. Now that has to be riskier than an international company actually promoting a product within specific guidelines’ (Manufacturer M-EU9, interview 2003).

The biggest companies active in developing tissue-engineered technologies are well represented in technical standards committees and in consultations about regulation. Most notable in this respect are the professional trade associations such as EUCOMED and EuropaBio who have lobbied extensively on the scope of proposed regulations (e.g., EUCOMED, 2003; EuropaBio, 2004). Increasingly stringent regulation will seek to extend technical standards within the hospital sector as well as industry. The extension of industry-endorsed standards to tissue users in national healthcare systems is intended to strengthen the overall purity of tissue practices, including in its ambit the increasing application of ‘engineering’ manipulations to human materials in public sector services. Alongside this, strategies of partitioning of new sectors are again evident, as in the expected exclusion of ‘traditional tissues’ from TE and in the attempted resistance to convergence with stem cell therapy.

### **Evidentiality: dirty data, difficult materials**

Innovation policy on new technology adoption in healthcare systems is increasingly influenced by the knowledge products of the new healthcare sciences (Faulkner, 1997; Timmermans & Berg, 2003). The methodologies for producing new healthcare knowledge are themselves the subject of attempts to create purer techniques where susceptibility to ‘contamination’ is reduced. The significance of the evidence-based movements in terms of purity/pollution has been noted by Traynor (2002). The research methods terminology, imported from clinical science and epidemiology, of ‘controlling for bias’, and the elimination of ‘contaminating’ variables is instructive here. The strictures of these increasingly refined methodologies are being applied to tissue-engineered technologies.

Below we present extracts and commentary suggesting the applicability of pollution ideas and partitioning concepts in the arena of the new evidentiality applied to regenerative medicine.

‘A lot of these trials are just locally recognised by local ethics committees and with standards for clinical trials that are sub-zero quality...they didn’t pay enough attention to the biostatistics.. one could judge that it’s not very ethical to run this trial because the power calculations.. have not been done properly..’ (Clinician CL-EU5, interview 2003).

‘.. when I looked at the literature seriously...it was all small case series and I see nothing to suggest that’s improved...they’re not even comparative studies. “I did these half dozen people and they got better. Isn’t it wonderful?”...that’s, I think almost inadmissible evidence, let alone poor evidence’ (Clinician CL01, interview 2003).

This position is a good representation of the importance that the healthcare sciences (health technology assessment, evidence-based medicine) have assumed in healthcare policy discourse. The need for pollution-free evidence is clearly expressed. Health technology assessment can be understood as a purifying, rationalist response to the dangers of unevaluated healthcare technologies (Faulkner, 1997). But such rational responses contend with a variety of different, often conflicting, ‘repertoires of evaluation’ in the design of healthcare policy and guidance (Moreira, 2005).

The discourse of evidentiality reaches also into the appraisal of the material safety of innovative technologies. The biological safety of TE technologies is taken to be of critical importance but ‘a consensus quality control programme to ensure that TE products work and are safe to use’ has not yet been established (Anonymous, 2000). In the absence of harmonised regulation, the types of evidence required to demonstrate safety are unclear. New standards and forms of testing are being sought. The report of a regulators/industry forum noted unresolved issues in evaluating emerging TE technologies including: need for ‘new assays; nontraditional animal models—e.g. transgenic animals, larger animals; relevance of new endpoints, e.g. genotoxicity and immunogenicity’ (ERA Consulting, 2003). Thus here we see pollution ideas associated with technical uncertainty, including a perception of a requirement for novel methods to assess new potential polluting risks.

The implementation of the TCD from 2006 will create a Europe-wide system for appraising, monitoring, reporting and accounting for any establishments procuring and processing human tissue for therapeutic purposes. The origin of human materials and the processing methods are subject to strictures for higher standards and new forms of evidence. This implies a far more stringent regime of information than has hitherto existed in most European countries.

Evidentiality and ethical standpoints may go hand in hand in shaping the regulatory innovation space for TE. An example was provided at an industry-sponsored ‘public hearing’ in January 2003 at the European Commission on proposals for the TCD. At this event a speaker was able to present an ‘evidence-based’ account, which considered questions of efficacy rather than safety, of a preference for adult stem cells as opposed to embryonic stem cells for tissue therapies (Prentice, 2003). Headlines included: ‘Claims for embryonic stem cells unsubstantiated’, ‘Ample evidence that adult stem cells show pluripotent capacity’ backed up by lists of scientific publications. The author revealed that he was a member of ‘Do No Harm: The Coalition of Americans for Research Ethics’, a Christian organisation, and was making a case for the unjustifiability of using embryonic stem cell therapy.

We can again note the importance of evidence of efficacy. In fact this representation of the science evoked explicit criticism. Several representations were criticised by European Commission officials

because they were focused on the *application* of TE technologies rather than donation and processing. This exemplified the tensions created by the apparent convergence of tissue banking and therapeutic application. Thus there was conflict not only over the public representation of TE science, but also over the agenda-shaping activity of participating stakeholders. EC officials sought to partition tissue and cell-sourcing discourse away from discourses of the societal *application* of technologies. This example, therefore, highlights the interpenetration of the jurisdictions of tissue *sourcing* (the TCD) and of *application* of TE (the TER).

### Publics’ and users’ values: ethical cleansing

Social and personal values are brought to bear in the policy discourse around tissue-engineering innovation. Ethical standpoints are evident in application to the other discursive arenas discussed here. A major impetus behind the regulatory movements has been the formal opinion produced by the EC’s specialist advisory group, the European Group on Ethics (EGE) in science and new technology, who stated in 1998 that there was an ‘urgent need to regulate the conditions under which human tissues circulate within the European Market’ (EGE, 1998). EGE principles are enunciated in some detail in the TCD, which quotes the four guiding principles: the ethical imperative to protect human health; the integrity of the human body; the free consent of donors; and the protection of identity. It also emphasises EGE’s backing donation as ‘a voluntary act of solidarity’. The preface to the directive notes that a survey of Member States revealed that ‘considerable discrepancies’ exist in national rules covering safety, quality and use of human tissues and that rules for authorisation and inspection of tissue procurement and banking activities were lacking in the majority. Thus regulatory measures to increase the purification of such activities were to be expected and have emerged in the subsequent directive. We see increased rigour in matters of donor consent and traceability of the source of donated tissues—autologous (donor and recipient same individual) technologies are construed as ethically cleaner than allogeneic (donor(s) and recipient(s) different) technologies; a trend that links the ethics of medical therapy with an ethic of clean evidence; an ethic that portrays (especially embryonic) stem cells as a socially ‘dirty’ area in comparison to



tissue-engineered technology. In some contexts, therefore, ‘safe tissues’ legitimated by good evidence are also ‘ethically purified’ tissues.

The following extract demonstrates a link between the discursive arenas of ethics and evidentiarity. It applies more to therapeutic application than tissue sourcing:

‘.. we’re looking at... a procedure [articular cartilage transplantation] for which there is no good evidence of efficacy or effectiveness.. I think the NICE [i.e. the then National Institute of Clinical Excellence—the UK central technology appraisal and healthcare guidance body] answer is a good start... saying they should *only be used in trials*, which means that then you’re saying to the patient, we’re either going to do this new fancy procedure that might work, or we’re going to do something else and we’re going to toss a coin—and that’s ok isn’t it? And I think that’s ethical... (Clinician UK CL-1, interview 2003) (author italics).

This points to the quarantining activity of a national healthcare system regulatory authority in patrolling the entry of a new TE technology into clinical practice. The technology is at the same time controlled *and* given a limited application to patients. It is important to note that this is an autologous application, a technology in which the patients’ own cells are expanded and re-implanted—seen in other contexts to be far *less* ethically contentious than some other TE applications (Faulkner, Geesink, Kent, & FitzPatrick, 2003; Kent et al., 2006a):

‘.. There is no ethical issue there if you are taking the patient’s own cells and using those cells to generate the patient’s own tissue the only time ethics would really come in is if you’re using gene transfer in that process. But even then I don’t think that’s a big issue. If you’re using allogeneic sources obviously there are scientific issues and then you have to ask the question then where are the cells coming from, who’s intellectual property is it, who’s cells are they? Did the donor know that they were actually donating those cells?...’ (Scientist advisor to European Commission, A-EU-6, interview 2003).

Major tension exists between regulation that would bring together ethical standpoints with ‘technical’ matters, and regulatory partitioning that would separate them. This has been illustrated

especially in the approach of the EC to the formulation of the TCD. The discussion above shows that the EC has sought to partition *contentious* ethical concerns away from the TE zone. Some members of the European Parliament have not been content with this. Views of patients’ advocates have also been opposed to this ethical purification:

‘...it is doubtful whether technical aspects can be completely held separate from associated ethical issues as implied by the proposal (i.e. the draft proposal for the TCD)... While I fully realize that different views on ethical aspects exist, I strongly disagree with the idea of leaving them simply untouched only because no consensus can be reached easily... In practical terms: harmonising technical regulations to maximise opportunities of human cell and tissue use but localising the ethical problems associated with it will eventually jeopardise the validity of the basic right of physical integrity in all European societies’ (Reimann, 2003, representing EURO-RDIS—European Organisation for Rare Disorders).

Nevertheless a principle of ‘ethical subsidiarity’ (our term), which leaves to national state authorities contentious ethical standpoints vis-à-vis the acceptability of using particular types of tissue or cell for research or therapeutic purposes, has been espoused by the European Commission. Thus in the arena of social values, in our first track of analysis using pollution ideas we observe increasing stringency in tissue sourcing, and in the second track—the devices of policy formation—we observe tension between technicality and values, and strategies aimed at the partitioning-out of dangerous technology, whether because of evidential uncertainty or ethical standpoints.

## Discussion

Human tissues and cells are increasingly being defined as commodifiable, commercialisable, regulatable technologies. They conjure up both hopes and dangers. The analysis outlined above suggests that there are competing constructions of the purity of tissue commodities and production processes. Attributions of purity/pollution shift depending upon the standpoint of actors. Thus what is ‘pure’ in one context may be seen (even by the same social actors) as ‘polluted’ in another. This was seen

above, for example, in the case of autologous cartilage transplantation which in the technology field may be regarded as ethically preferable to donor-cell technologies (and is thus ‘purer’), but in the context of healthcare system evidentiality was portrayed as unacceptable (and is thus ‘polluted’). Similarly, hybrid technologies may be seen as impure from particular moral standpoints, while ‘natural’ human tissue (‘classical tissue’) may be seen as impure/dangerous from the standpoint of actors such as industry who claim credibility via participation in technical standards. Industry perceives itself as cleaner than the hospital sector. On the other hand the use of ‘classical tissues’ has been the domain of the healthcare system, and here the implication of the public value of integrity of the body is that unmanipulated tissue for medical treatment is safer and purer than engineered tissue. Such effects are to be expected and are reminiscent of the shifting frames of social description analysed in a different context by Buckley (1984).

Industry and regulators, in particular, are struggling to establish the parameters of a clear TE technology zone. The transformation of human tissue into commodities is relevant to the potential development of a technological zone. The establishment of such zones is of large political and economic consequence (Barry, 2003, p. 25). In his analysis, Barry argued that legal and political disputes over property and their subjects/objects are also disputes about the re-configuration of technological zones. Our analysis suggests that ‘tissue engineering’ is a loosely defined, unstable technological zone. The recent proposal to re-categorise tissue-engineered technology as an ‘advanced therapy’ under the centralised *medicines* regime in Europe (EC DG Enterprise & Industry, 2005) may be contrasted with the USA where TE is moving more toward a medical devices regime (Hogle, 2005), which would be considered less stringent. In this discussion, we have illustrated the regulatory/innovation actions of industry, EC policymakers and regulators, patients representatives, clinicians and scientists, and found common purificatory trends and common strategies in their diverse policy-related actions.

The four arenas of regulatory policy discourse and activity discussed above are, of course, themselves interlinked. Indeed it is at the boundaries where different arenas of discourse and value meet, that some of the most acute tensions are to be seen.

This paper furnishes a number of examples of this. Evidentiality and governance are becoming more closely linked in contemporary health-related social processes. Information and its social use as ‘evidence’ have a regulatory function that is emphasised in forms of governance that can be characterised as the ‘regulatory state’. Strathern (1999) and Majone (1997), from the different perspectives of social anthropology and public policy studies, have pointed to the regulatory role of information. And in analysis of medical technology innovation, the regulatory role of the new healthcare sciences has been shown (Faulkner & Kent, 2001; Lehoux & Blume, 2000; May, Mort, Mair, & Williams, 2001). Key tensions were also apparent in the EC/EU debate on the TCD in which discourses of commerce and ethics came into conflict. This is seen for example in the issue of not-for-profit donation. In a further example, the social management of the tension between evidentiality and ethics can be seen in the strategic containment of unproven technologies within the boundaries of clinical trials.

Our analysis of regulatory developments illustrates a growing Europeanisation of human tissues and cells and biomaterials as a tradeable technology, and of engineered tissue as a technological zone. Standards and their surveillance are reaching further into the technology and the healthcare system. Europe as a trade area is partly constituted by regulatory and standard-setting activity, as we have seen in the partitioning processes observed above. In the case of sourcing of human tissue technology, regulatory standardisation takes the form of a framework that allows national variation on some important dimensions, such as ethical standpoints vis-à-vis certain types of animal or human tissue. Transnational technical standards appear to be promoted to a greater extent than do ethical standards. This is likely to support the development of technological markets and the circulation of technical knowledge and expertise within them. As Barry suggests:

‘In general, those objects and practices that are considered scientific or technical are precisely those which...escape territorial constraints’ and... ‘making a technical practice more “social” or “cultural”...may serve to restrict its movement’ (Barry, 2003, pp. 38–9).

This highlights the importance of examining the process of technical standards, especially where they

might be less open to public view, as in the EC ‘comitology’ process being applied to TE regulatory movements. Thus the inoculating process of regulatory partitioning and the purification trends described above primarily serve the corporate and EU politico-economic interests of transnational industry zone-building.

Public policy in Europe faces a shift towards more risk averse and more stringent regulatory policies (Vogel, 2001, p. 1). We are witnessing a trend toward the ‘purification’ of therapeutic technology and its sources, associated with the increased use of human tissues and cells and the development of engineering of tissues and cells. Alongside the increasingly stringent response to pollutions, we have also shown the sometimes contested partitioning processes in the classificatory ordering of a TE zone. Pollution practices and classificatory partitioning work can be seen in the material innovation of TE technology, in the social and organisational processes of regulation itself, in the discourses of evidentiality and commercialisation, and in debate about social values. The four arenas of discourse considered here can be seen as constitutive of the societal ordering and valuing of tissue-engineered technologies under conditions of increasing human, animal and material malleability, complexity and risk. Whether the trends toward increasing delineation and regulatory purity will engender public confidence in TE remains an open question.

We end on a speculative note. If these partitioning processes and pollution ideas express a ‘general view of the social order’, à la Douglas, it is perhaps to support the sense of a highly differentiated but highly interlinked nexus of shifting relations of society, technology and nature. In this nexus socio-material boundaries are dynamic and contested, and it is at the boundaries that concepts of pollution and partitioning are most salient. The permeability of boundaries can be observed in an old depiction of a ‘primitive world view’ consisting of ‘Physical forces...interwoven with the lives of persons. Things...not completely distinguished from persons, and persons... not completely distinguished from their external environment’ (Douglas, 1966, p. 107), which has certain parallels with contemporary theorisation of a complex, risky, interconnected form of life in hybrid notions such as socio-technology, social ecology, citizen science, risk society, and biosociality.

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## References

- Anonymous (2000). Tissue Engineering. *Nature Biotechnology*, 18(Suppl.), IT56–58.
- Appadurai, A. (1990). Disjuncture and difference in the global cultural economy. *Theory, Culture and Society*, 7(2–3), 295–310.
- Barry, A. (2003). *Political machines: Governing a technological society*. London: Athlone Press.
- Bock, A. K., Ibarreta, D., & Rodriguez-Cerezo, E. (2003). *Human tissue-engineered products: Today’s market and future prospects—synthesis report EUR 21000 EN*. Institute for Prospective Technological Studies IPTS and Joint Research Centre EC.
- Bowker, G. C., & Leigh Star, S. (2000). *Sorting things out: Classification and its consequences*. Cambridge: MIT Press.
- Brown, N., & Michael, M. (2004). Risky Creatures: Institutional species boundary change in biotechnology regulation. *Health, Risk and Society*, 6(3), 207–222.
- Brown, N., & Webster, A. (2004). *New medical technologies and society—reordering life*. Cambridge: Polity Press.
- Brown, N., Faulkner, A., Kent, J., & Michael, M. (2006). Regulating hybrids: ‘Making a Mess’ and ‘Cleaning Up’ in tissue engineering and transpecies transplantation. *Social Theory & Health*, 4(1), 1–24.
- Buckley, A. D. (1984). Walls within walls: Religion and rough behaviour in an Ulster community. *Sociology*, 18(1), 19–32.
- Bud, R. (1995). In the engine of industry: Regulators of biotechnology, 1970–1986. In M. Bauer (Ed.), *Resistance to new technology: Nuclear power, information technology and biotechnology* (pp. 293–310). Cambridge: Cambridge University Press.
- Cox, M., & Tinkler, J. (2000). Biomaterials regulation: innovative products—outgrowing the European Framework? *Action for Biomaterials*, May 2000, The Biomaterials Partnership.
- Department of Health. (2000). *Guidance on the microbiological safety of human organs, tissues and cells used in transplantation, advisory committee on the microbiological safety of blood and tissues for transplantation*. London: Department of Health.

- Department of Health. (2001). *A code of practice for tissue banks providing tissues of human origin for therapeutic purposes*. London: Department of Health.
- Douglas, M. (1966). *Purity and danger: An analysis of concepts of pollution and taboo*. London: Routledge & Kegan Paul.
- EC (European Commission). (2004). Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. *Official Journal*, L102, 48–58.
- EC (European Commission) DG Enterprise. (2004). *Proposal for a harmonised regulatory framework on human tissue engineered products: DG Enterprise Consultation Paper, 6 April 2004*. Presented at stakeholders' conference, 16 April 2004, Brussels.
- EC (European Commission) DG Enterprise & Industry. (2005). *Human tissue engineering and beyond: proposal for a community regulatory framework on advanced therapies*. Consultation paper. European Commission, 4 May 2005. <<http://pharmacos.eudra.org/F2/advtherapies/docs/ConsultationPaper-AdvancedTherapies-2005-May-04.pdf>> [accessed July 2005].
- EC (European Commission) DG Sanco. (2003). *Amended proposal for a European and Council Directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells*. COM (2003) 340 final May 2003. <[http://europa.eu.int/eur-lex/en/com/pdf/2003/com2003\\_0340en01.pdf](http://europa.eu.int/eur-lex/en/com/pdf/2003/com2003_0340en01.pdf)>
- EC (European Commission) Health & Consumer Protection Directorate-General. (2004). *Draft: Technical requirements for the donation procurement and testing of human tissues and cells* (03.08.2004).
- EC (European Commission) Health & Consumer Protection Directorate-General. (2005). *Draft: Technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells* (29.03.2005).
- EGE (1998). European Group on Ethics in Science and New Technologies. Ethical aspects of human tissue banking. Opinion no.11. Brussels: European Commission.
- ERA Consulting. (2003). *Discussion forum: Development and regulation of cell-based therapies. Report of meeting*. London: ERA Consulting.
- EU (2003). *Parliament debate on the proposal for a European Parliament and Council directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells*. Strasbourg 9 April 2003. <http://www.europarl.europa.eu/activities/expert/cre/search/go.do> [Accessed June 2006].
- EUCOMED. (2003). *Eucomed response to European Commission DG Enterprise consultation document 'Need for a legislative framework for Human tissue engineering and tissue-engineered products'*. <<http://www.eucomed.be.org/?x+4&y=11&z=218>> [accessed January 2003].
- EuropaBio. (2004). *EuropaBio feedback on commission's consultation paper on tissue engineered products legislation*. <<http://www.europabio.org/positions/Posengineering.doc>> [accessed July 2005].
- Faulkner, A. (1997). 'Strange bedfellows' in the laboratory of the NHS? An analysis of the new science of health technology assessment. In M.-A. Elston (Ed.), *Sociology of medical science and technology* (pp. 197–223). Oxford: Blackwell.
- Faulkner, A., Geesink, I., Kent, J., & FitzPatrick, D. (2003). Human tissue engineered products—drugs or devices? *British Medical Journal*, 326, 1159–1160.
- Faulkner, A., & Kent, J. (2001). Innovation and regulation in human implant technologies: developing comparative approaches. *Social Science & Medicine*, 53, 895–913.
- Faulkner, A., Kent, J., Geesink, I., & FitzPatrick, D. (2004). Purity and the dangers of innovative therapies: Re-ordering regulation and governance in the shaping of tissue-engineered medical technology. *Paper presented to EASST/4S conference 'Public Proofs'*, École des Mines, Paris.
- Franklin, S., & Lock, M. (Eds.). (2003). *Remaking life and death—towards an anthropology of the biosciences*. Santa Fe: SAR Press.
- Gabe, J. (1995). Medicine, health and risk: The need for a sociological approach. In J. Gabe (Ed.), *Health, medicine and risk: Sociological approaches* (pp. 1–18). Oxford: Blackwell.
- Geesink, I., Faulkner, A., Kent, J., & FitzPatrick, D. (forthcoming). Technoscience and frames of risk in the regulation of tissue engineered technologies in Europe. *Science as Culture*, in review.
- Hogle, L. (2005). Emerging forms of evidence in regenerative medicine. *Presentation to innovative health technologies workshop at health technology assessment international annual conference*, 20–22 June 2005, Rome.
- Jallali, N. (2003). Tissue engineered products need improvements in quality. *British Medical Journal*. <<http://bmj.bmjournals.com/cgi/eletters/326/7400/1159#33239>>; 12 June 2003 [rapid response, accessed 18.06.04].
- Kent, J., Faulkner, A., Geesink, I., & FitzPatrick, D. (2006a). Towards governance of human tissue engineered technologies in Europe: Framing the case for a new regulatory regime. *Technological Forecasting and Social Change*, 73(1), 41–60.
- Kent, J., Faulkner, A., Geesink, I., & FitzPatrick, D. (2006b). Culturing cells, reproducing and regulating the self. *Body & Society*, 12(2), 1–23.
- Kong, Y. T. (2003). The need to regulate human tissue engineered products: ophthalmology perspective. *British Medical Journal*. <<http://bmj.bmjournals.com/cgi/eletters/326/7400/1159#32999>>; 5 June 2003 [rapid response, accessed 18.06.04].
- Lehoux, P., & Blume, S. S. (2000). Technology assessment and the sociopolitics of health technologies. *Journal of Health Policy, Politics and Law*, 25(6), 1083–1120.
- Majone, G. (1997). The new European agencies: Regulation by information. *Journal of European Public Policy*, 4(2), 262–275.
- May, C., Mort, M., Mair, F., & Williams, T. (2001). Factors affecting the adoption of tele-healthcare in the United Kingdom: The policy context and the problem of evidence. *Health Informatics Journal*, 7, 131–134.
- MDA (Medical Device Agency). (2002). *A code of practice for the production of human-derived therapeutic products*. London: Department of Health.
- Moreira, T. (2005). Diversity in clinical guidelines: the role of repertoires of evaluation. *Social Science & Medicine*, 60(9), 1975–1985.
- Prentice, D. A. (2003). Scientific basis for cell and tissue therapy. *Presentation to public hearing on the proposal for a directive of on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells*, January 2003, Brussels. <<http://www.eutop.de/ct/>> [accessed February 2003].

- Reimann, A. (2003). *Statement provided at the hearing on the patient view to the proposed directive on quality and safety of human tissues and cells*, 29 January 2003, Brussels. <<http://www.eutop.de/ct/>> [accessed February 2003].
- Strathern, M. (1999). *Property, substance and effect: Anthropological essays on persons and things*. London: Athlone Press.
- Timmermans, S., & Berg, M. (2003). *The gold standard: The challenge of evidence-based medicine and standardization in health care*. Philadelphia: Temple University Press.
- Traynor, M. (2002). The oil crisis, risk and evidence-based practice. *Nursing Inquiry*, 9, 162–169.
- UKXIRA (United Kingdom Xenotransplantation Interim Regulatory Authority). (2003). *The UKXIRA fifth annual report*, January 2002–September 2003. London: Department of Health.
- Vogel, D. (2001). *The new politics of risk regulation in Europe*. CARR discussion paper no. 3, August 2001. London: LSE. <[http://www.lse.ac.uk/Depts/carr/Publications\\_folder\\_web\\_files/Disspaper3.pdf](http://www.lse.ac.uk/Depts/carr/Publications_folder_web_files/Disspaper3.pdf)> [accessed September 2003].
- Welsh, I., & Evans, R. (1999). Xenotransplantation: Risk, regulation and surveillance. *New Genetics and Society*, 18(2/3), 197–217.