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Editorial

Welcome to the first issue of Genomics, Society and Policy, a peer-reviewed open access online journal examining social aspects of developments in Genomics and implications for policy. In a fast moving field such as Genomics, discussions of social and policy aspects frequently need to take place at an early stage. The length of time to paper publication sometimes counts against appropriate and timely impact of debate. Hence we believe that an online journal is particularly valuable in this field.

GSP has been developed within the ESRC Genomics Network in the UK. The Network was established by the UK Economic and Social Research Council in 2002 and consists of CESAGen (ESRC Centre for Economic and Social Aspects of Genomics: a Lancaster-Cardiff collaboration), Egenis (ESRC Centre for Genomics in Society, Exeter), Innogen (ESRC Centre for Social and Economic Research on Innovation in Genomics, Edinburgh), the ESRC Genomics Survey (Surrey) and the ESRC Genomics Policy and Research Forum (Edinburgh). In developing this journal, we have formed a partnership with the Dutch Centre for Society and Genomics, leading to the editorial collaboration. We are delighted to have formed links also with the network of Genetics Knowledge Parks funded by the Department of Health in the UK; and that we have persuaded key figures internationally to join the editorial board.

We are grateful to the Wellcome Trust who funded some of the early development work on the journal, to the ESRC, to all colleagues who have supported this initiative in its early stages especially Michael Parker at Ethox, and to all the contributors to the first issue, which presents a collection of papers on the special theme of 'Human Tissue, Epidemiology and Ethics'.

GSP will appear three times a year and we welcome submissions on any aspects of Genomics, Society and Policy. We hope to hear from you.

RUTH CHADWICK

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Ethical Challenges of Genomic Epidemiology in Developing Countries

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Abstract

Ethical challenges in genomic epidemiology are the direct result of novel tools used to confront scientific challenges in the field. An orders-of-magnitude increase in scale of genetic data collection has created the need for establishing diffuse international partnerships, sometimes across developed- and developing-world countries, with ramifications for assigning research ownership, distributing intellectual property rights, and encouraging capacity-building. Meanwhile, the fact that genomic epidemiological research is so far upstream in the pipeline of therapy development has implications for the privacy rights of research participants and for a rigorous definition of valid informed consent, particularly in resource-poor settings. From these scientific underpinnings, we distill out two main categories of ethical issues: (1) How should researchers ensure that the subjects of research are appropriately protected? and (2) What is the structure of an equitable and fair system for distributing the financial and scientific rewards of research? We attempt to delineate the contours of specific problems in each category and propose steps toward solutions with reference to a particular project, known as gMap.net, that focuses on genomic epidemiological studies of malaria.

Introduction

Infectious diseases constitute a significant global burden, particularly to those in poverty. Almost six million people die of HIV, malaria, and tuberculosis each year.[1] Simultaneously, a revolution in genomics has created high hopes for important breakthroughs in our understanding of the molecular mechanisms of disease pathogenesis. Several observers have argued that a special effort must be made to ensure that the genomics revolution does not bypass but rather is duly harnessed for the fight against global diseases of poverty.[2,3]

Part of this special effort is ensuring that genomic studies conform to ethical standards of medical research. However, just as the field of genomics is fraught with novel scientific challenges, it is also unique in the ethical challenges that it poses to researchers, particularly those working in developing countries. There exists an abundance of principles for the ethics of biomedical research in developing countries, but few validated methods by which to apply those principles. This article aims at that void, describing the ethical issues raised by genomic epidemiology, with an eye towards specific problems encountered in organizing a genomic database for malaria research (www.gMap.net).

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What does genomic epidemiology have to offer?

The sequencing of microbial pathogen genomes provides information on targets for diagnostic tests, mechanisms of virulence, and tactics used by pathogens to evade host defenses. Similarly, it is believed that genomics will yield a better understanding of differential susceptibility and response to infectious diseases in humans as well.[4] For instance, considerable progress has recently been made in identifying a number of gene families which are involved in modifying susceptibility to malaria. Both research strategies – investigating the genome of the pathogen and the genome of the host – promise benefits for the alleviation of global diseases of poverty through the development of drugs and vaccines.

In particular, effective vaccines may provide the best hope of a sustainable reduction in the mortality of HIV, malaria, and tuberculosis.[5] The facts that (1) people who are repeatedly exposed to infection acquire some level of immunity and (2) some people resist infection better than others leads to the hypothesis that it should be possible to develop effective vaccines against these three infectious diseases. The missing link is that we do not yet understand the molecular basis of acquired immunity or natural resistance. Hence, genomics, with its potential for elucidating these processes at the molecular level, holds such hope for vaccine development.

Of course, genomics is no panacea – it will not instantaneously reduce the global burden of infectious diseases. The viruses, parasites, and bacteria respectively responsible for HIV, malaria, and tuberculosis are highly evolved human pathogens skilled at evading the immune system. Nevertheless, the information harvested using genomic methods will enable us to investigate diseases in novel ways. One such method is known as genomic epidemiology. While past genetic studies have been successful at discovering major genetic defects of the immune system – mostly due to a rare mutation of a single gene – genomic epidemiology seeks to uncover genetic variants with a much more modest effect on disease susceptibility.[6] Why are scientists concerned with these weaker genetic effects? There are two main reasons. First, even a modest genetic effect may be of considerable public health importance if it acts on an extremely common disease, and if many different genes make a modest contribution then the overall genetic effect may be huge. Second, even modest association with specific genetic variants may be sufficient to gain insights at the molecular scale of disease pathogenesis, leading to new strategies to treat or prevent the disease.

There are a few essential elements to a genetic epidemiological study. Because the genetic effects of interest are relatively weak, a large sample size – with thousands of affected individuals matched with population controls – is required. For similar reasons, studies must be undertaken across different populations as well. At the other end of the spectrum, high-throughput genotyping technology is required to screen as much of the genome as is possible for each individual. Therefore, innovative algorithms and informatics resources must tackle the analysis of genomic diversity in different populations and fine-scale mapping of genetic association.

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What is novel about the ethical issues that arise in genomic epidemiological studies?

To answer this question, it is necessary to step back one level and examine the implications of the novel scientific tools utilized in genomic epidemiology that were described above. Three implications are readily drawn. First, consider the orders-of-magnitude increase in scale of data collection for genomic epidemiology. The ramifications of this increase in scale include a need for diffuse partnerships, which bring with them problems of standardizing ethical review, assigning and sharing intellectual property rights, and dividing research ownership. The second and third implications are manifestations of the fact that genomic epidemiological research is so far upstream in the pipeline of therapy development. Flowing from this is the requirement that consent be obtained for use of patient samples in future research projects, the details of which are unknown at the time of sample collection. Finally, there is a group of challenges surrounding the future social consequences of genomic research. These are particularly important because of the intuition that there is something very personal about an individual's genetic code. Because the potential uses of genomic information cannot be well defined, the potential abuses are similarly nebulous; this is what makes them difficult to prevent.

The nature of this last implication – future social consequences of genomic research – makes it worth going into some detail on the scope of this article. Societal decisions on applications of research, such as whether genetically-modified humans should be permissible, are not addressed here. Rather, we concern ourselves with two main problems: (1) protecting the subjects of genomic epidemiological research and (2) designing an equitable and fair system for allocating financial and scientific rewards of research.

Protecting subjects of research

Informed Consent. There are several sets of guidelines on the ethics of research related to healthcare in developing countries.[7,8,9] For example, the principle of informed consent, codified in the Declaration of Helsinki, has been established as a cornerstone of biomedical research ethics.[10] However, complications arise in applying these guidelines to practical situations.[11,12] It is at a specific intersection of these two areas – achieving informed consent for genetics research in developing countries – where the difficulties of implementing established principles are perhaps most evident.

We can distill a number of guiding principles from a review of major reports[13,14,15] and notes from the field:[16,17,18]

- When appropriate, provide information to potential research participants in group meetings. Information should be communicated over a period of time rather than in one meeting.
- The primary source for information about a research project should be health workers rather than physicians.
- Unfamiliar concepts should be explained using analogies.

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- Comprehension assessment should be a routine part of the informed consent process.
- Community consent should be respected, and, when appropriate, should be sought out, but is not a sufficient substitute for individual informed consent.

While these principles are helpful, they are only tangentially related to a number of impediments one encounters in genomic epidemiological research. For instance, is it acceptable to ask for open-ended permission to study every gene in a person's body? This question is germane because the great power of genomics is that it allows us to investigate the role of genes whose function we don't currently know. In other cases, guidelines are too vague to provide much help in solving a realistic dilemma. Unfamiliar concepts should be explained using analogies – but how does one even gauge comprehension of concepts such as a gene or DNA? Is it ethical to simply explain, "We are studying attributes that you inherited from your parents?" Finally, some questions raise the idea that perhaps informed consent is not the only ethical principle that is relevant: what are researchers' obligations for samples that were given for genetic studies five years ago, before it was considered feasible to do whole-genome analysis? Do the benefits of research ever outweigh the costs of not following up with donors to obtain re-consent?

In struggling with these issues, gMap.net collaborators are working toward a policy of sensible informed consent. Although the problem of composing appropriate consent forms is very pertinent, the organizing principle of our discussions has been that sensible consent is a process rather than a document.[19] The informed consent process is divided into two discrete stages: education and validation. Education requires both long-term interventions (e.g., working with particular members of a community to germinate an understanding of genetic research in that community) and short-term solutions (e.g., pictorially representing the process of infection by a mosquito). Validation corresponds to each stage of the education process – from checking local language translations to administering an exam testing comprehension. We group the categories of problems that have been encountered in the field using the classical framework of 'valid' consent as the union of (1) disclosure and comprehension of information, (2) voluntariness, and (3) competence.[20]

Disclosure and comprehension of information. Language and conceptual comprehension barriers are well-established in the informed consent literature.[21] In genomic epidemiology, one of the most intractable challenges is how to convey genetic concepts. We have proposed guidelines to work with linguists for both local-language translation and for word creation. Word creation involves relating a concept like 'gene' to attributes of heredity that are already understood in the local language. To increase understanding, creative didactic methods – such as showing the scale of how much blood is being taken from a child's body – should be employed as far as possible. At the point of communicating why consent itself is required, a clear distinction should be made between research data collection and clinical care. Comprehension assessment of consent should be used to both validate and refine these methods. Finally, the brevity of consent forms and meetings was emphasized as no less important for gMap.net than for other settings.

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Voluntariness. The distinction between research data collection and clinical care is important in itself. The predicament here is that, in resource-poor settings, the provision of healthcare in research projects acts as an undue inducement, violating the criterion of voluntariness that is an essential element of informed consent.[22] Given the nature of our data collection – blood for DNA samples is collected during adverse malaria episodes, often from children – it is almost impossible to separate research from treatment. Our guideline therefore is to explicitly accept that the criterion of voluntariness fails in this case because other principles take priority. A corollary is that we must take steps to minimize inducement effects, such as fully ensuring that potential subjects know that healthcare provision is not contingent on participation.

Another set of problems related to voluntariness of genetic research revolves around the question of how far consent applies to future research. At the time that consent is given, the participant has no way of knowing exactly what research projects he or she is consenting to.[23] One idea that has surfaced is to narrow the scope of possible research by a disease-specific constraint – that is, participants who give their consent to a research collaborator are assured that their sample will only be used for malaria-related projects, for instance. This could be combined with a continuous opt-out process by which participants can withdraw from any study at any point in time in the future. One limitation of this approach is the logistical difficulty of continuously communicating what research projects are being conducted using a given person's genetic information.

Competence. There are two particular problems relating to vulnerable populations and competent consent which we must address: (1) At what age is it appropriate for an adolescent to veto a parent's consent (i.e., to give assent)? and (2) How do we ensure that a participant's competence is not undermined by severe illness? Our thinking on obtaining assent from adolescents has evolved from specifying an age threshold to charging the investigator (again, with review from a local ethics board) with examining individual cases based on the criteria of maturity and understanding. To ensure that a patient's competence is not compromised by severe illness, it has been proposed that a two-stage consent process be implemented. The first stage is simply obtaining consent for taking blood when a patient comes in for treatment during a malaria episode. The second stage is following up with the patient (or the patient's parents or guardians, in the case of children) to ensure that permission was indeed granted for the blood to be used in research. That way, the decision to participate in research is not made when the potential donor's faculties may be affected by severe illness.

The final category of problems revolves around the issue of conflicts between social units – for instance, an individual, a family, an ethnic group, or a local government – for granting consent. The only definite principle to have emerged in the literature is that community consent is no substitute for individual informed consent. There is no precise guidance on *when* community consent should be sought out. In our discussions, we proposed that the investigator – with review from the local ethics board – should decide which social units beyond the individual should be consulted. It was also proposed that each social unit consulted has veto power; that is, only if all social units grant consent can it be considered sensible.

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Confidentiality. Anonymity and confidentiality of research participants are safeguards against the potential harm arising from misuse of genetic information, such as discrimination, stigmatization, and procedures as practical as unwanted paternity testing.[24] It is important to be clear about levels of confidentiality in genetic databases. We follow the structure outlined by the American National Bioethics Advisory Commission (NBAC) in distinguishing the extent to which a research sample can be linked with the identity of its source.[25] "Unidentified" samples are originally collected without identifiers and are impossible to link with their sources. "Unlinked" samples are those that were originally identified, but have been irreversibly stripped of all identifiers and thus impossible to link to their sources. "Coded" samples are unidentified for research purposes, but can be linked to their sources through the use of a code. Decoding is the responsibility of the principal investigator or another designated researcher. "Identified" samples are those that allow the researcher to link the biological information derived from research directly to the individual from whom the material was obtained.

Aside from ethical directives for protecting participants, the source of genetic material and the purpose of research drive the decision regarding what level of identification is appropriate. Again, novel characteristics of genomic epidemiological research shape the ethical discussion. Collaboration in gMap.net occurs between developing-world laboratories largely responsible for collecting DNA samples and developed-world laboratories responsible for high-throughput genotyping of those samples. A pragmatic approach to confidentiality might be to code samples both during sample collection and again during processing of samples received in the developed-world genotyping center. The lab code and field code would not be able to be linked up except by the principal investigator in the genotyping center. Making the link all the way back to the name of the sample contributor requires the willing participation of the principal investigator of the developing-world laboratory from which the sample originated. From this description there is no difficulty in classifying this structure as "coded" confidentiality. However, there are issues that escape the NBAC framework given above. For instance, how much phenotypic information—which is necessary for disease-specific genomic epidemiological studies—can be stored with a "coded" sample before it effectively becomes an "identified" sample?

In some circumstances, there are reasons to have "coded" rather than "unidentified" or "unlinked" samples. The long-term nature of genomic epidemiological research might require that further information—or re-consent—be collected from participants for future studies. Although there should be a high threshold for re-tracing the steps back from a genotyped sample to the contributing individual—and this threshold should be guarded by researchers as well as local ethics committees—the possibility of doing so should not be completely precluded. It is worth mentioning also that despite best intentions and efforts in ensuring confidentiality, modern DNA identification techniques can link a sample with an individual if one wishes to spend the effort and the individual provides a sample for matching.[26] Taken together, these parameters argue for a confidentiality policy that accomplishes the twin goals of protecting participants and facilitating research. It has been suggested that the best way to do this is to adopt a 'charitable trust' model where encryption of identifiers is one step removed from researchers themselves.[27]

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Finally, there are two issues regarding protection of participants which we have omitted discussion of here. First, we have not addressed the informed consent process for archived samples which may have been taken from subjects who were not made specifically aware that the samples were going to be used for genetic studies. Practical guidelines to regulate these archived specimens—in almost all circumstances they can be used only after they have been unlinked—have been developed and explained elsewhere.[28] Second, we have not given details on database access conditions here because problems of database management will be addressed in the next section.

Financial and scientific rewards

Data access and intellectual property rights. Policies governing data access to DNA sequences span a broad spectrum. At one extreme, private firms generate data that are used internally or licensed to pharmaceutical companies for hefty fees. For example, in 1996, the company Human Genome Sciences sold exclusive rights of access to its database of cDNAs for three years to SmithKline Beecham for $125 million.[29] Private genetic databases, therefore, are effectively unavailable to most potential users because of licensing terms and nondisclosure agreements. While the sequence data in private databases may eventually contribute to therapeutic development, their utility as an academic research tool is necessarily limited. Proponents of these private databases counter that their advantage lies in attracting private capital to help develop practical applications of genetic research. Indeed, selling exclusive rights to database access leads to a neat interface with the normal framework for development in the pharmaceutical sector – intellectual property rights. Companies like SmithKline Beecham are able to mine private databases for 'patentable' sequences; the patenting of DNA sequences then provides the incentives necessary for subsequent development.

At the other end of the spectrum are the 'Bermuda Principles,' named after the agreement on data release reached by the International Human Genome Sequencing Consortium in Bermuda during 1996.[30] The major government- and nonprofit-funded high-throughput sequencing centers originally agreed to the Bermuda Principles in order to ensure rapid sequence data release. Updates to the Principles called for release of DNA sequence assemblies of 2 kb or greater within 24 hours of generation and of raw shotgun sequence data within one week of generation. It was believed that without such an agreement, the wait for information sufficient to meet patent criteria would lead to long delays and thus be a significant impediment scientifically.[31]

The Human Genome Project also had to address two problems created by its novel data release policy. The first problem was breaches in scientific etiquette involving pre-publication data. Several papers submitted to peer-reviewed journals using data made available by the Human Genome Project did not acknowledge the contribution of the producers of that sequence data. To address this, Project leaders made clear that publications are expected to acknowledge the source of sequence data through the use of appropriate citations; they also urged the broader scientific community to recognize that producers of sequence data have a legitimate interest in publishing their own data.[32] The second problem was operationalizing the belief that the genome should not be patented. Project leaders added an explicit directive in 1997 against

patenting newly discovered DNA with the threat of penalizing researchers in future grant reviews if the directive were not obeyed.[33] It should be noted that the Project chose this route rather than filing noncommercial patent applications to block other claimants or putting restrictions on who could access the public database.

Policies on access to genetic databases that lie intermediate to these two ends of the spectrum have also emerged. The SNP Consortium, funded by a group of 11 private companies collaborating with research centers and the Wellcome Trust, aimed to create a collection of sequence differences in the human genome. Just as with the Human Genome Project, collaborators had a commitment to produce a publicly-available end product—in this case, a human genome map of single nucleotide polymorphisms (SNPs) of a certain density. The members of the Consortium agreed that while the SNP map itself should not be patentable, any innovations made using data from the Consortium was fair game for patenting.[34] The SNP Consortium also employed a unique approach to keeping data in the public domain. The Consortium applied for patents, but only to establish a priority date for the discovery and secure standing as inventors, not to secure commercial patent rights.[35] Such patents are sometimes called 'blocking patents' because they serve the purpose of obstructing other claimants' potential patent filings. Patent applications were abandoned before they were actually issued, making it clear that their sole purpose was to ensure open access to the SNP database.

Another genetic variation resource, the International HapMap Project, also utilized innovative methods to protect open access for its database. Just as with the Human Genome Project and the SNP Consortium, the coordinators of the HapMap Project did not believe that the resource which they sought to catalogue should be patented.[36] However, the HapMap Project employed a distinct strategy to fend off restrictive patents that would hinder their efforts toward open access. This strategy developed as a result of a specific problem related to the nature of the data compiled by the HapMap Project. One can broadly divide this data into two sets: (1) SNPs, SNP assays, allele and genotype frequencies by population, and haplotype information and (2) genotype information in a chromosome region that is of insufficient density to derive haplotype information. HapMap's data access policy mandates that the former set of data be released to public databases as quickly as possible with no restrictions.[37]

However, the latter set of data required a more complicated access tool. The reason for this is that it would be possible for external parties to combine the public HapMap Project's genotype with their own, to then construct haplotypes, to file for patents on those haplotypes, and thereby restrict others from using those haplotypes and underlying data.[38] In order to defend against this possibility, genotype data is made available under a 'click-wrap' license agreement, which is a type of 'copy-left' license.[39] This provision mandates that users are granted access to all data only if they agree not to restrict use of the data by others and to share the data only with others who have agreed with the same condition. When genotype information is of a sufficient density to construct haplotypes, then the individual genotypes and haplotypes are publicly released (both on the HapMap website and to dbSNP, a public SNP database with no licensing restrictions). The HapMap data access policy also specifically mentions that the 'click-wrap' licensing approach is not meant to block

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downstream patents on haplotypes for which associated phenotypes, such as disease susceptibility, have been discovered.[40]

These trends toward rapid pre-publication release of data from large-scale biological research projects crystallized in a meeting on data sharing sponsored by the Wellcome Trust in January 2003.[41] Meeting participants embraced the spirit of the Bermuda Principles. The report issued as a result of the meeting argues that the benefits of pre-publication release of sequence data have been significant and that therefore rapid, open access should be the standard pursued in other large-scale projects. 'Community resource projects' were defined as those devised to create a set of data, reagents, or other material "whose primary utility will be as a resource for the broad scientific community."[42] The report also specifically addressed the issue of conflicts between pre-publication data release and the norms of publishing the first analysis of one's own data. One solution brought forth was to create a new type of scientific publication known as a Project Description to inform the scientific community about the project and to provide citations to reference data sources.

It is worth going a bit deeper in examining whether the recommendations of the Wellcome Trust meeting apply to genomic databases involving developing-country partnerships. One can distill out three main issues in such an analysis:

- The importance of the positive-feedback nature of databases, that is, to what extent overall progress of the enterprise depends on rapid release because results build on one another
- Research credit, that is, publications or patents taken out to recognize researchers responsible for particular discoveries
- 3rd party development, that is, implications for downstream exploitation of basic science research

Figure 1 (see end of paper) shows how existing database access policies address these three issues. Here, we seek to go beyond that in order to point up difficulties that arise particularly in a developing-world context for genomic epidemiology.

The first issue, the positive-feedback nature of databases, is an important filter – if results do not build on one another in some way, a distributed collaboration does not have to agree to standards of rapid pre-publication data release. It is likely that many genomic epidemiological databases, such as gMap.net, do satisfy the positive-feedback criterion because of the large sample sizes required for studies.

A review of the data access policies of the community resource projects mentioned to this point (the Human Genome Project, the SNP Consortium, and the HapMap Project) reveals that the positive-feedback problem was most likely the dominant factor in the construction of those policies. However, for the developing-world context, the second and third issues, research credit and 3rd party development, increase in significance. Research credit (described more fully below in the *Research Ownership* section) is important not just for individual scientists, but for capacity-building aims as well—publications establish the reputation of scientists, which is important in attracting funds to a growing lab. Web publication of data yields neither resume building through publications nor intellectual property rights. Thus,

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considerations for research credit have ramifications for exactly how rapid data release should be – and indeed whether it should be 'pre-publication' at all.

3rd party development, or downstream development of basic science research, is a thornier issue still. There are a number of factors at play here. Some are logistical: how does one assign patents in large collaborations where there is no single firm assignee? Others are more fundamental. The case of genomic epidemiology again breaks from the precedents we have examined in that disease-specific projects like gMap.net will include disease association studies, going beyond map- or sequence-building to the discovery of specific genetic variants that cause resistance or susceptibility to disease. This would seem to move towards the domain of patentable innovations. Of course, database projects must take into account that at some point compiled data must interface with intellectual property regimes, no matter how open-access initial data sharing is. The added challenges for diffuse genomic epidemiological projects are manifold: Which party holds the intellectual property? Where are patent rights taken out? What steps should the network take to ensure that research is translated into therapeutic innovation as quickly as possible? Do researchers have a responsibility in ensuring that sample populations have access to these fruits of research? To whom should the financial rewards, such as royalty revenue, flow?

The most elegant solution to the data access problem seems to be encapsulated in the Bermuda Principles – placing data immediately without restriction into the public domain. This line of reasoning gains force because fundamentally the data yielded by association studies are descriptions of natural phenomena very similar to human genome sequences. However, a cogent argument can also be made in favor of upstream proprietary rights – even for projects that are fully publicly-funded – because the network could thereby have more leverage over what occurs downstream in the process, such as ensuring access, sharing benefits, and ensuring expeditious development. A range of intermediate solutions to these problems may also be emerging as the open-access research movement begins to interface with public or nonprofit drug- and vaccine-development initiatives.[43]

Benefit sharing. Here, benefit is an umbrella term for therapies developed by genomic epidemiological research and financial rewards that might be derived from those therapies. International guidelines that speak to how these benefits should be shared with research participants have often incorporated some form of an 'assured availability agreement'—a guarantee that those exposing themselves to the risks of research be assured access to the products of that research.[44,45] As Bhutta has pointed out, there is considerable complexity in trying to put these principles into practice.[46] In the case of genomic epidemiological research, there is substantial lag time between data collection and the development of therapies. There are connections with the issue of protecting subjects: (1) the promise of benefits might act as an undue inducement to an impoverished population and (2) any obligation to assure availability of an end product to original participants impinges upon the confidentiality of the database. It is also unclear who deserves to gain financially from, for instance, the discovery of a novel anti-malarial molecule from studies of natural genetic diversity. Any of at least five groups can make a claim: the subjects themselves, the health professionals who diagnosed and treated them, the

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epidemiologists who managed the study, the geneticists who produced the result, and the company that makes the end product. As Chadwick and Berg have pointed out, while our moral intuitions may sympathize most with the subjects' claim, it is the scientists who have actually made the subjects' samples 'valuable.' [47]

But this leads us to deeper issues which are also at work here. Genomic epidemiology describes the relationship of patterns of disease with natural human diversity. If we assert first that the reference human genome sequence belongs to mankind and second that, given the positive-externality effects of vaccines and therapies for infectious diseases, research is of potential benefit to all, it follows that the aims of benefit-sharing should shift from purely local interests to broader interests.

Nevertheless, companies may have special moral obligations to local participants, and perhaps more broadly to local healthcare systems. Keeping in mind the more expansive view of benefit-sharing, a social return to the community might take the form of technology transfer, local training, provision of healthcare or information infrastructures, or the possible use of a percentage of royalties for humanitarian purposes. For example, the Human Genome Organization Ethics Committee proposed that pharmaceutical industries should set aside a certain proportion of their income for healthcare development or as broad humanitarian assistance for developing countries.[48] Such a set-aside has the added advantage of skirting the difficulties, both logistical and ethical, of tracing back to research participants after a number of years have elapsed.

Another idea that draws on this broader conception of benefit-sharing is the idea of a 'developing country license.'[49] The idea originated in efforts to convince universities to adopt publicly-minded licensing policy. Policies dictated that universities' intellectual property rights would be leveraged to ensure access to essential medicines, such as anti-retrovirals, in resource-poor countries. Similarly, the organizers of a genetic database could mandate the adoption of such 'reach-through' licensing provisions for any research conducted using the group's data. Provisions could ensure access to end products for the broad geographic areas in which original research participants reside. Ethical guidelines developed for the Human Genome Diversity (HGD) Project serve as precedent here.[50] The HGD Project requires that financial benefits from commercial use of samples and of the information derived from them should be in some way returned to the community. Only those researchers who agree to this clause are granted access to the HGD Project's samples and data.

Research ownership. Consider the structure of a collaboration for an international malaria genomic database. Laboratories in the developed world must establish partnerships with research groups doing large-scale clinical and epidemiological studies of malaria in developing-world locales. The developed-world labs must develop pipelines for high-throughput genotyping of thousands of DNA samples as well as database technologies to share that data directly with the developing-world research partners. At some point in the future, the database would be sufficiently populated for very large-scale studies across multiple sites (e.g., requiring 10,000 samples from patients with severe malaria) to dissect complex genetic effects. This structure immediately leads to fundamental questions regarding ownership: how is credit distributed among research partners? How are implications for local capacity-

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building and career development incorporated into that calculus? What sort of mechanism should be in place to deal with conflicting results?

The Swiss Commission for Research Partnership with Developing Countries contends that the organizing principle here should be capacity-building.[51] It is not that research ownership is important as an end in itself, but rather as a means to garner increased funding or human capital. For that reason, there should be discussion amongst collaborators as to what types of research ownership are most important in developing local capacity—publication in journals, inclusion on grant proposals, or technical training. In the gMap.net group, there are links being formed between the African labs and the Oxford labs via student exchange and periodic meetings. The distributed nature of analysis in gMap.net—genotyping data are made directly available to researchers via the web—facilitates the mission of capacity building. It is hoped that these processes will grow into a governance structure that can handle the more significant challenges of diffused research ownership, such as how to deal with conflicting opinions on scientific findings.

Conclusions

We have attempted to review some of the ethical challenges confronted in doing genomic epidemiological research in developing countries, to describe the guidelines currently in place to help resolve those challenges, and to outline novel elements of genomic epidemiological research that require further ethical analysis. To conclude, we point out some limitations of the perspective which we have adopted in this article. First, because we have divided the issues into discrete categories – for example, issues of informed consent and issues of data access – there has not been an emphasis on the interconnections between categories. For instance, does the level of consent granted set constraints on who is able access a particular database? That is, if the criterion of consent is that it be disease-specific, does that necessitate that data access be given only to those researchers confirming that their interest is in that disease? The logistical difficulties of such an inference are self-evident. Another limitation of our focus is that we have ignored broad areas of ethical complexity in an attempt to make progress on particular problems. Improving local capacity in bioethics in developing countries is essential to ensure that the philosophical principles of genomic ethics are informed by a practical understanding of what will work at the local level.

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Figure 1

Data access policies for genetic databases	Private databases	SNP Consortium	HapMap Consortium	Updated Bermuda Principles (Human Genome Project)
Positive-feedback nature of databases: overall progress of enterprise depends on rapid release because results build on one another	- Feedback process hindered by access limitations such as user fees	- Public-private consortium involved collaboration across research entities that involved commitment to publicly available SNP map	- Conditional rapid data release policy to the public via dbSNP. Only genotype information that could be used to file patents restricting the access of others is subject to 'click-wrap' agreement.	- Sequence assemblies larger than 2 kb must be released into public databases within 24 hours; raw shotgun sequences must be released within a week.
Research credit: publications or patents taken out to recognize researchers responsible for particular discoveries	- Not applicable; individual researchers' rewards are financial rather than publication- or patent-related	- Since data was immediately released publicly via a website, intermediate publications were not applicable. Patent applications were taken out solely to establish the dates of scientific discoveries but are abandoned after a period sufficient to prevent others from filing patent applications using Consortium data.	- Since data is immediately released publicly via a website, intermediate publications are not applicable. No patent applications are filed on discoveries.	- Other researchers are permitted to use publicly available data for all purposes aside from "publication of the results of a complete genome sequence assembly or other large-scale analyses." No patent applications are filed on discoveries.
3rd party development: implications for downstream exploitation of basic science research	- Interfaces with intellectual property milieu almost immediately; companies pay for access to private databases in order to mine them for 'patentable' sequences	- SNP Consortium founders believed that the SNP map that would be developed is itself not something that should be patentable. However, there are no restrictions on patents taken out using SNP data as a result of, for instance, association studies.	- The HapMap Consortium believes that SNP, genotype, and haplotype data in the absence of specific utility do not constitute patentable inventions. However, data-release policy does not block users from filing for appropriate intellectual property on, for instance, association studies as long as any ensuing patent is not used to prevent others' access to HapMap data.	- One part of the Bermuda principles (revised in 1997) is an explicit directive to participants against patenting newly discovered DNA. However, there are no conditions placed on users of the GenBank database; nor are blocking patents filed by the Project. As with SNP and HapMap data, there are no restrictions on patents taken out using Project data.

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Informed Consent and the Bio-banking of Material from Children

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Abstract

This paper considers the ethical issues raised by biobanking of material from children who are not mature enough to give ethically valid consent. The first part considers consent requirements for entry of such materials in the biobank, whereas the second part looks at the issues that arise when a competent child later wants to withdraw previously stored materials, and at the issues that arise when there is informational entanglement between information about a parent and information about a child. The paper argues for three main conclusions:

1. That it is in most cases acceptable for parents to give proxy consent to entry of material from their children into biobanks, even though this is not strictly speaking in the best interest of the child;
2. that a right to withdraw from the biobank is more important when material has been entered with proxy consent; and
3. that disputes about the withdrawal of entangled information, i.e. information that is both about a parent and a child, should be resolved in favour of the child.

Introduction

This paper will consider the ethical issues raised by biobanking of material from children who are not mature enough to give ethically valid consent (i.e. who are incompetent to consent)[1] [2]. The first part will consider consent requirements for entry of such materials in the biobank, whereas the second part will look at the issues that arise when a competent child later wants to withdraw previously stored materials.
The standard view in the research ethics literature and the international declarations is that children, like other incompetent persons, can only be included in research projects that 1) cannot be performed with competent persons as research subjects, 2) are in the best interest of the child (or only minimally against their interest), and 3) has been consented to by a relevant proxy decision-maker. It is further generally assumed that the children's' parents should be the proxy decision-makers.
This standard view is, for instance expressed in paragraphs 24-26 of the most recent revision of the Helsinki Declaration from the World Medical Association:

> "24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the

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> population represented and this research cannot instead be performed on legally competent persons.
> 25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
> 26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate."[3]

Very similar provisions can be found in the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine:

> "Article 17 –Protection of persons not able to consent to research
> 1. Research on a person without the capacity to consent as stipulated in Article 5 may be undertaken only if all the following conditions are met:
> i. the conditions laid down in Article 16,sub-paragraphs i to iv, are fulfilled;
> ii. the results of the research have the potential to produce real and direct benefit to his or her health;
> iii. research of comparable effectiveness can not be carried out on individuals capable of giving consent ;
> iv. the necessary authorization provided for under Article 6 has been given specifically and in writing; and
> v. the person concerned does not object .
> 2. Exceptionally and under the protective conditions prescribed by law, where the research does not have the potential to produce results that directly benefits the health of the person concerned, such research may be authorized subject to the conditions laid down in paragraph 1,sub-paragraphs i, iii, iv and v above, and to the following additional conditions:
> i. the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition;
> ii. the research entails only minimal risk and minimal burden for the individual concerned."[4]

The consensus is quite clear that the person who can give informed consent to become a research participant is the paradigm case and research on persons incapable of giving consent is an aberrant case that must be accommodated within the consent

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paradigm, if it is at all to be allowed. The consensus has been developed in the context of clinical research, but has later been extended to all kinds of biomedical research[5].

This accommodation is achieved by seeking a "consent equivalent" and by restricting the types of research that persons incapable of consenting can participate in. The restriction on types of research can be justified in three partially different ways.

The first is based on the historical fact that vulnerable groups have often been used in ethically problematic research and that if the incompetent could be used as research participants in ordinary projects there is a risk that they would become an easy source of research material.

The second focuses on the intersection of interests between the person with a specific condition and the group of sufferers with that condition. The argument is that even if a person does not realize a personal benefit from the research, he is benefited indirectly through the benefits accruing to the group. However, this justification is problematic in many cases where group membership is not stable (e.g. where the group identifier is a phase and not a state sortal). One situation where the argument is of doubtful validity is where the membership of the group in question is temporary and where most persons who are part of the research will no longer be members of the group when the benefits materialize. This could for instance be the case for children if a disease only afflicts a particular age group, or where a condition is rapidly progressive, or where research projects are very drawn out in time. Another such situation is where the benefits are of a kind that can only be enjoyed by people who are not yet members the group. This could for instance be the case if the knowledge sought in a project is exclusively knowledge about how to prevent the occurrence of the condition.

The third possible justification is the pragmatic one embraced by those who would really like to ban all research on children, but who realize that unless we allow some kinds of research without informed consent into conditions where all sufferers are incompetent, very little progress will be made in the treatment of such conditions (the "golden ghetto" argument), but such research should be limited to those projects that cannot be performed in any other way in order to minimize the infringements caused by research without consent.

All three justifications of restricting research to problems shared by the group in question are problematic in various ways, primarily because it is much easier to provide an argument for a complete ban on research using incompetent research subjects if one proceeds within the consent paradigm, than it is to provide an argument for this particular way of restricting research.

Best interest

What kind of interests of a child is it allowable for a proxy decision-maker to take into account when considering the child's participation in research projects?

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It is generally assumed that in order for research on children to be ethically justified a higher level of scrutiny by research ethics committees, and closer attention to the details of the proxy consent given by parents, guardians or others is necessary. Many justifications can be (and have been) given for this difference between research in children and research in competent adults, and some of these are quite plausible. It is, for instance, quite plausible that proxy decision makers may in certain contexts underestimate the negative effects of pain and discomfort on children, or that children sometimes may be an easily exploitable pool of research subjects.

One way to protect against these abuses or to resolve these problems is to require proxy decision makers to make their decisions according to the best interest of the child. Since much of biobank research has no direct benefits for the research participants themselves this would seem to indicate that the research cannot be in the best interest of the participants and that proxy decision makers therefore cannot legitimately permit or consent to participation on behalf of a child. The arguments against the legitimacy of entering children into research then usually claim that research offering no "direct benefit treats the child merely instrumentally, as a means to the ends of others. [6]

But in real life we do accept that parents[7] can make a whole range of decisions for their children. We like to maintain that these decisions should always be made in the best interest of the child, but in practice we allow parents to make decisions that are clearly not in the best interest of the child[8] For example parents make decisions to bring children up in polluted and dangerous cities, they expose them to danger as pillion passengers on bicycles in busy traffic, they deny them the protection of the triple vaccine for measles mumps and rubella on the most fragile of fears about its safety compared with the palpable dangers of contracting any of these childhood diseases, or they are weighing the interests of one child against the interests of other children in the family (e.g. when choosing where to go on holiday).

We may try to hide this practice by claiming that the decisions we allow are in the long term best interest of the child, or that they are in the best interest of the child as defined by the parents, but this is often just obfuscation. It is obvious that the interests of others are allowed to play a role, and in many cases the proxy decision maker is fully aware of this fact. Is this legitimate and can it be extended to the research context?

According to the seminal work of Buchanan and Brock the best interest principle should be understood in the following way:

> "The best interest principle states that a surrogate is to choose what will best serve the patient's interests, in other words, that which will maximally promote the patient's good. The qualifier "best" indicates two important factors: Some interests are more important than others in that they make a larger contribution to the patient's good, and a particular decision may advance some of the patient's interests while frustrating others. Thus, according to the best interest principle, the surrogate must try to determine the net benefits to the patient of

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> each option, after assigning weights reflecting the relative importance of various interests affected when subtracting the "costs" from the "benefits" for each option."[9]

The main problem in applying this principle is in defining what counts as "the patient's good". The principle ostensibly prevents a parent from taking account of the good of others, for instance the good of other family members or the good of the parent him or herself. It therefore protects the child against the obvious danger of parents making decisions primarily based on their own interests.

But on closer inspection the principle does not actually specify how we are to identify the interests of the child.

Do children for instance have "moral interests", i.e. interests in being treated as moral agents who want to discharge their moral duties? I have, with John Harris, argued that this is indeed the case and that there is no reason to presume moral turpitude in our children[10]. It may be a fact that children are psychological egoists, but just like in adults this is no reason to organise society as if egocentric interests are the only ones that they really have. Current restrictions on the use of children as research participants are therefore, in our view, to tightly drawn.

Children, data and sample collection

Let us move to the more concrete question of data and/or sample collection from children for research projects that have no possibility of helping the cohort of children who are the research participants. Under what conditions will a broader conception of "best interest" allow such research?
We should perhaps first note that if the data collection is very burdensome or painful for the child this may in itself rule out participation. But even in cases where the data collection is not burdensome or painful issues concerning privacy, ownership, personal integrity and future possible harm, broadly conceived, still remain.

How important are these issues, is the mere fact that some research uses identifiable samples and therefore in some sense breaches privacy sufficient to show that it is not in the child's best interest? On a strict definition of best interest it clearly is, because even a minimal breach is still a breach, but there seems to be no good reason why a parent should not be allowed to authorise this minimal transgression of the best interest standard, when parents are allowed to authorise many other transgressions.

This may sound like opening the floodgates to misuse of children as research subjects, so it is important to say something more precise about under what conditions parents should be allowed to consent to research that is not in their child's strict best interest.

These conditions are probably best approached *via negativa* by identifying situations where parents should not be allowed to give consent. This class of situations will include instances where[11] 1) the parents' have strong interests in the research going ahead that are not shared with the child, 2) the breach of privacy is not only

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"technical" (i.e. privacy is breached in relation to the researchers) but public (i.e. privacy is breached in relation to people in the child's personal sphere), 3) the breach of privacy is continuing over time or is irreversible[12], 4) the research is likely to generate findings that will impact negatively on the child, 5) the cumulative effect of participation in longitudinal research exceeds reasonable limits, for instance because of repeated testing or sample giving.

These situations fall into three categories, one concerned with the interests of the parents themselves, one with the size of the burden and the breach of best interest, and one with the irreversibility of decision-making. Whereas research ethics committees can deal with the two last issues in their general assessment of a given project, the first issue is often only detectable at the level of individual proxy decision-makers and it will therefore be the responsibility of the researchers to exclude children where parents are deciding from their own interests and not from a consideration of the interests of the child.

If we compare these restrictions with current biobank research projects we will see that it is in most cases justifiable for parents to give proxy consent for their children.

Withdrawing from the biobank

It is, however, worth looking in more detail at the question of possible future harm (clause 4. above), because biobank samples from children may be analysed at any time during their life time, and beyond. We are therefore debating possible personal harms from such analysis that may fall within the next 90-100 years, and posthumous harms that extend indefinitely. I have discussed the issues raised by research use of samples from the dead extensively in two already published papers[13], and will therefore here only look at the possible personal harms during the lifetime of the persons in question. These may be of two kinds:

- Harms directly created by the analysis of the person's sample in the biobank
- Harms created by attribution of certain negative or stigmatising characteristics to a group to which the person belongs as a result of biobank research

The first kind of harm occurs when information is created which negatively affects the person in question, e.g. information about genetic disorders, or about the person's genetic lineage.

The second kind of harm occurs when biobank research links some negative or stigmatising characteristic with a group to which the person belongs or identifies with by showing and making public that this characteristic is more prevalent in that group[14].

Whether or not these kinds of harms are likely to (or will) occur cannot usually be determined at the outset of a biobank project. Completely new analytical or statistical techniques may be developed that enables completely new and unforeseeable research questions to be pursued.

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We may argue that this is not a problem in so far as the person in question is warned about this during the original consent process, and knowingly donates tissue anyway; and some[15] might even argue that it should be possible to give up your right to withdraw your sample and data from the biobank, if you are well informed and know what you are doing.

In the case of material from minors entered into the biobank with proxy consent, the situation is, however different. Like all proxy decisions, a decision to renounce withdrawability is a decision I make on behalf of someone else. As argued above there is nothing inherently wrong in making irreversible decisions for children that are not in their strict best interest, but there is something wrong about making a decision irreversible that could just as well be reversible at the point when the child reaches decisional competence. There can be no reason, apart from the convenience of the researchers, to renounce withdrawability completely at the proxy consent stage.

We know that children when they grow up often differ from their parents with regard to preferences and values, and we do therefore have good reasons not to close off decisions that do not need to be closed off. This is the main thrust of Joel Feinberg's well known "right to an open future" argument[16].

Allowing a full right of withdrawal to the competent child, whose materials have been entered into the biobank with proxy consent, is therefore more important than allowing a full right of withdrawal to adult donors to the biobank.

Some specific withdrawal issues when information is entangled

Some specific issues concerning withdrawal of consent, data and samples occur in cases where there is what we can call "informational entanglement" in relation to data and samples held in the biobank and relating ostensibly to two different persons. This is regularly the case for data in parent-child cohort studies and for samples in biobanks containing placental tissue.

The entanglement in the placental tissue case is biological as well as informational. Knowledge about the size and condition of the placenta at birth gives us information about both mother and child, and the placenta is itself an intricate mix of tissues derived from both the mother and the foetus[17]. What should be the effect if one of the parties involved in creating the placenta withdraw consent to its continued storage? As long as the child is still incompetent this will in most cases not raise any practical problems, since the mother will be the proxy for the child, and will presumably also withdraw on behalf of the child[18]. But what if the child is now competent and there is disagreement concerning withdrawal?[19]

Saying that each has a right to withdraw based on the normal considerations concerning self-determination, creates the problem that we could as well argue for a right to continue in biobank research based on the same considerations. We therefore have a conflict of two rights with the same underlying justification. The mother could

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claim that she was the one who gave initial consent and that she therefore has a primary claim to decide what should happen, but this will not solve the problem in this case because she did not only consent for herself, but also as a proxy for her child. We could just as well argue that the now competent child should have decisional primacy because her or she was not directly involved in the initial decision and should be given a chance to "correct" the decision of the proxy decision-maker. None of these two arguments for giving priority to one of the conflicting parties is particularly strong, and we therefore need to look for another solution.

In the case of pure informational entanglement we could try to disentangle the information, for instance by deciding piece by piece, who the information primarily concerns, and allow the primarily concerned person to decide. This approach is, however, not without problems, because some pieces of information are essentially about several persons. It is a fact about me that my mother is a nurse, that she is Danish etc., as well as these things being facts about her. Even for pure informational entanglement we can therefore not avoid giving an answer to the question about how to resolve disagreements about withdrawal of entangled information.

Here it is worth noting that we have always allowed some kinds of informational entanglement in questionnaire studies and databases. It is, for instance, seen as unproblematic to ask about and register a partner's or spouse's age, occupation or even congenital disorders, without seeking the informed consent of that person.

It is clearly possible to mount an argument that this is problematic (at least slightly). From the fact that I have told you my private information, does not follow that I have given you permission to give this information to anyone who asks. Without there being a full and explicit confidentiality and disclosure agreement between us, there will still be an implicit agreement about what information you can divulge and to whom. These implicit rules concerning the passing on of information revolves partly around harm and embarrassment, but also involves "need to know" and "closeness" considerations. These implicit rules still hold *vis-à-vis* researchers who cannot presume a right to get second hand information, but in most cases the information asked for and stored is of a kind that I can legitimately disclose about my family members to outsiders.

I claimed above that the right to withdraw from and the right to continue in research have similar justifications, but could it not be argued that they do not have the same strength? In the clinical research context the right to withdraw is, as mentioned above absolute, but there is no generally recognised right to continue in research[20]. It is, however, again important to note the differences between biobank research and clinical research. The issue of disputed entangled information involves the rights of two research participants against each other, not primarily against the researchers, whereas the similar rights in the clinical context are rights the participant hold against the researchers.

I don't think that there is a principled way of resolving this conflict, except that we may take cognisance of the fact that in the case of entanglement between parent and

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child there is an asymmetry in the way the entangled information has been entered into the database or biobank. Whereas the information about the parent is there with the person's own, personal consent, the information about the child is there only with proxy-consent. Based on this asymmetry we can argue that disputes over withdrawal of entangled information, that cannot be resolved in dialogue between parent and child, should be resolved in favour of the child. If the now mature child wants to withdraw his or her information the information should be withdrawn, and if they want their information to remain it should remain, whether or not it is entangled with information about their parents.

Conclusion

In this paper I have argued for 3 conclusions:

1. That it is in most cases acceptable for parents to give proxy consent to entry of material from their children into biobanks, even though this is not strictly speaking in the best interest of the child;
2. that a right to withdraw from the biobank is more important when material has been entered with proxy consent; and
3. that disputes about the withdrawal of entangled information, i.e. information that is both about a parent and a child, should be resolved in favour of the child.

As long as one keeps the significant differences between biobank research and clinical research in mind, none of these conclusions should be particularly controversial.

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[1] I will omit discussion of exactly when children become ethically competent to consent, and just note that I think that this happens a long time before they become legally competent in most countries.

[2] In this paper I use arguments developed through many years of discussions with my colleague John Harris. I have worked so closely with John that it is sometimes difficult to know where my ideas end and his begin. I hope that I have not been guilty of excessive plagiarism. Some of the ideas have previously been discussed in the context of clinical research in: J. Harris and S. Holm. Should We Presume Moral Turpitude in Our Children – Small Children and Consent to Medical Research. Theoretical Medicine 2003; 24: 121-129.; in S. Holm. Autonomy, Authenticity, or Best Interest: Everyday Decision-Making and Persons with Dementia. Medicine, Health Care and Philosophy 2001; 4: 153-159.; and in S. Holm, 2004. Conducting Research in the Alzheimer Disease Population: Balancing Individual, Group, Family and Societal Interests. In Ethical Foundations of Palliative Care for Alzheimer Disease. R. Purtillo and H.A.M.J ten Have, eds. Baltimore. The Johns Hopkins University Press: 320-329.
My thinking on these issues has also been greatly stimulated by participation in a workshop arranged by Dr. Lisbeth Knudsen as part of a research network sponsored by the European Commission, DG-Research (EUROPEAN NETWORK ON CHILDREN'S SUSCEPTIBILITY AND EXPOSURE TO ENVIRONMENTAL GENOTOXICANTS (QLK4-CT-2002-02198))

[3] World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975,35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

[4] Council of Europe. 1997. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine.

[5] It is of considerable interest that this very strong requirement for consent arose first in medical research and that it is not yet accepted in many other branches of research with humans. This might lead one to believe that something specific to medical research lies behind this strong emphasis on consent. That medical research often involves bodily intervention and often creates risk of physical harm are two obvious candidates for distinguishing specific features of medical research. These features are absent from much of biobanking research, or the bodily intervention is minimal and/or performed by the research subjects themselves (e.g. taking a mouth swab).

[6] See for example P. Ramsey. 1970. The Patient as Person. New Haven, CT. Yale University Press, 11-19.; P. Ramsey. Children as Research Subject: A Reply. Hastings Center Report 1977; 7: 40.; and P. Ramsey. The Enforcement of Morals: Non-Therapeutic Research on Children. Hastings Center Report 1976; 6: 24. In an interesting review of these issues Lainie Friedman Ross suggests that parents may, if there is minimal risk, enter children into research because their entitlement so to do is part of parental autonomy rights. (L.F. Ross.1998. Children, families and health care decision making. Oxford: Clarendon Press, Chapter 7).This claim will not be further discussed here.

[7] We will here focus on parents as proxy decision-makers but the arguments that follow are valid for most other kinds of proxy decision makers as well.

[8] This is, for instance, rather obvious in cases where there is more than one child, but limited resources and where maximising the interests of one child will negatively affect the interests of the other child.

[9] A.E. Buchanan and D.W. Brock. 1989. Deciding for others - The ethics of surrogate decision making. Cambridge: Cambridge University Press, 94.

[10] Holm & Harris, op.cit. note 3.

[11] This is probably not an exhaustive list and not all situations in the list are equally problematic.

[12] Strictly speaking every breach of privacy is irreversible except in situation where it is literally true that ”if I tell you this secret I will have to kill you afterwards”. In normal life information cannot be withdrawn, e.g. if I have told you that our mutual friend Bill is impotent, I cannot later retract that information, because there is no reliable technique by which you can erase the information from your memory.
But in biobank cases this does not hold, since stored information is stored in a fully erasable medium and is usually not remembered by any person because although it may have been entered onto the system by a person, this will have been just one of many sets of data entered.

[13] S. Holm and R. Bennett R. Genetic research on tissues stored in tissue banks. ISUMA:Canadian Journal of Policy Research 2001; 2: 106-112.
S. Holm. The Privacy of Tutankhamen – Utilising the Genetic Information in Stored Tissue Samples. Theoretical Medicine 2001; 22: 437-449.

[14] The following is a non-genetic example but illustrates the problem. If exam results after secondary school are correlated with first names it is found that there are reasonably strong relations between exam results and names. The top names of the list are, as could be expected girls’ names (we know that girls generally do better in school than girls), but more importantly in the present context is that there is a correlation between having a mis-spelt first name and having low exam grades. Thus having a name like “Jonahtan” is linked to having low grades. Although this can easily be explained through a concept like “social inheritance”, i.e. having parents who can’t spell is likely to influence your educational achievement, it is probably not a finding that most would think of in advance. Thus this research project has created a new stigmatising feature.

[15] Including myself in work in progress.

[16] J. Feinberg. 1992. Freedom & Fulfillment – Philosophical Essays. Princeton, NJ. Princeton University Press.

[17] Similar issues are potentially raised in research on, and storage of blood samples from pregnant women since we know that these regularly contain foetal cells in such quantities that attempts have been made to use the foetal cells from this source for prenatal diagnosis, see for instance L. Jackson. Fetal Cells and DNA in Maternal Blood. Prenatal Diagnosis 2003; 23: 837-846.

[18] We can of course imagine situations where the mother and father are estranged and the father has the parental rights, but I will leave aside direct discussion of these, presumably rare situations, since they are morally isomorphic to discussions involving disagreements between the mother and the competent child.

[19] Informational entanglement may also occur between siblings, monozygotic twins being the limiting case where there is complete entanglement of genetic information, but in this paper I will only discuss the parent-child cases.

[20] But there is a right to continue receiving effective experimental treatment after a research project has ended. See paragraph 30 of the Helsinki Declaration, op.cit., note 4.

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Biomedical Research and the Commercial Exploitation of Human Tissue

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Abstract

There is widespread anxiety about the commercialisation and commodification of human tissue. The aims of this paper are: (a) to analyse some of these concerns, and (b) to see whether some of the main ethical arguments that lie behind them are sound. Part 1 looks at 'inducement arguments' against paying individuals for their tissue and concludes that these are generally quite weak. Part 2 examines some ethical objections to third parties (e.g. biotechnology companies and researchers) commercially exploiting human tissue. Firstly, it is argued that prospective tissue donors should be given very full information about the extent to which their tissues will be commercially exploited and about the financial interests of tissue collectors and researchers, since this is an essential component of valid consent. Secondly, some doubt is cast upon the (widely held) view that while 'the human body and its parts shall not, as such, give rise to financial gain', intellectual property based on human tissue research is generally acceptable[1]

Introduction

> … the commercialization of human tissues … raises a host of … social, cultural, religious, and psychological issues on the meanings we assign to the human body and, in particular, on how we treat it during life and after death. Many people conceptualize the transfer of human organs and tissues during life or after death as a gift motivated by altruistic feelings, not economic incentives. They believe that the buying and selling of human biological samples debases the value of human life, is antithetical to the gift paradigm of tissue transfer, can lead to further oppression of the disenfranchised and the poor, and is an affront to the dignity of donors and their families.[2]

> … the commodification of human cells, tissues and organs incites particular concern because boundaries usually assumed to be natural and inviolable are inevitably transgressed, raising concerns about 'self' and 'other', 'identity', 'genealogies', group continuity and so on.[3]

As these opening quotations suggest, there is considerable anxiety about the commercialisation or commodification of human tissue. My aims in this paper are (a) to analyse some of these concerns, and (b) to see whether the main ethical arguments and principles that lie behind them are sound. The expression 'human tissue' can be used very broadly but I will focus here mainly on the use of human tissue samples in biomedical research. Also, for reasons of space, I'll focus solely on tissue taken with consent from living competent adult donors. Taking tissue from dead bodies, from children, and from incompetent adults raises difficult additional ethical issues which

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can't be satisfactorily dealt with here. The commercial exploitation of human tissue raises a large number of ethical questions but, for our present purposes, the most pressing ones are: 'should research subjects be paid for their tissue?' and 'is there anything wrong with third parties (e.g. biotechnology companies) commercially exploiting human tissue?'.[4] The remainder of this paper is divided into two parts, each dealing with one of these questions.

[1] Should Individuals Be Paid For Their Tissue?

According to the Medical Research Council (MRC):

> … research participants should never be offered any financial inducement to donate samples. Payment of reasonable expenses or costs is however acceptable.[5]

This is very much the orthodox view and expressions of it are ubiquitous. For example, the Nuffield Council on Bioethics also tells us that:

> Payment to donors of tissue should cover only reasonable expenses and should not act as an inducement … [and] rewarded gifting is unacceptable…[6]

In this part of the paper, I review some of the main arguments for this view, focussing in particular on the idea that payment, or excessive payment, may invalidate the consent of the tissue donor. I'll call this the Inducement Argument because the central idea is that payment may constitute an 'undue inducement' to take part in research.

In order for a consent to be valid, three main elements must be present (and present in sufficient quantities): information, competence and voluntariness.[7] The Inducement Argument against paying tissue donors focuses mainly on the last of these, voluntariness. As the Nuffield Council on Bioethics puts it:

> … [a] factor which may affect the voluntary nature of consent to research is any inducements accompanying invitations to participate in research.[8]

Although this is a widely held view, saying why we should believe it isn't easy. Here are some possible reasons.[9]

> (a) Financial incentives encourage people to do things that they wouldn't otherwise do
>
> (b) Financial incentives encourage people to do things that are likely to be harmful to them and which go against their 'better judgement'
>
> (c) Financial incentives can be make people's actions and decisions less autonomous or non-autonomous.

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(a) and (b) seem to be what the General Medical Council has in mind when it instructs doctors:

> … not [to] offer payments at a level which could induce research participants to take risks that they would otherwise not take, or to volunteer more frequently than is advisable or against their better interests or judgement …[10]

(a) however seems problematic. For the fact that payments encourage people to do things that they otherwise wouldn't clearly doesn't, in and of itself, invalidate consent. For, if it did, then consent problems would be endemic and would occur every time someone was encouraged by payment to go to work for wages or to hand over property in return for a price. So while it can be conceded that some subjects wouldn't contribute tissue if it weren't for the money, this fact alone in no way invalidates their consent.[11]

(b) is in some ways more plausible. Or at least it is plausible to suppose that we ought not to expose research subjects to more than a certain level of danger and ought not to encourage them, as the GMC puts it, to 'volunteer more frequently than is advisable'. Admittedly allowing payment (especially generous payment) does make it possible for there to be a class of 'professional' research subjects who expose themselves to excessive risk.[12] The fundamental problem, though, is not payment per se but rather the fact that the subjects are exposed to too much danger. So provided that we could find a way of controlling the risk, perhaps through a licensing or registration scheme for research subjects, this worry about payment would not arise. Of course, there would inevitably be practical problems to overcome since would-be 'professional research subjects' may well try to subvert any safety systems put in place, but (in principle, at least) payment is not itself the primary problem.

This thought is bolstered by two further considerations. First, for any individual research project, the level of risk remains the same regardless of whether or not payment takes place. So if someone objects to paying subjects on the grounds that payment will encourage excessive risk-taking, she ought to object to the research project itself, not just the payment. An illuminating analogy is someone who objects to paying soldiers on the grounds that it encourages people to do something excessively dangerous. Surely we should say to such a person that, if the objection is excessive danger, then she should object to military service in general, not (just) to paid military service. Much the same goes for paying tissue donors. If the real worry is risk, we should object to dangerous research of all kinds, not just the paid variety.

Second, it is by no means obvious that monetary incentives make people act, as the GMC suggests, "against their better interests or judgement". Indeed, this is a rather surprising view to take since, in ordinary life, people are expected to trade off monetary gains and losses against other harms and benefits on a daily basis, and trading and employment require us constantly to do such reckoning. So if an adequately informed person decides, after deliberation, that it is worth subjecting herself to a certain risk in return for £1000 then we should not just assume that she is acting against her better judgement since, for all we know, the £1000 is more valuable to her than avoiding an x% risk of physical harm.

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My impression is that sometimes what happens when we think about this issue is that we discount or ignore the prospective research subject's (often entirely sensible) desire for money, along with the (closely related) fact that having extra money will benefit her. This in turn leads us to think (mistakenly) that taking part in research is only in accordance with a person's "better interests or judgement" if she would have been willing to participate for free, or if doing so for free would be in his best interests. But this is a peculiarly demanding criterion to use, not least because it is not one that we would apply in any other context. After all, most people wouldn't go to work if it weren't for the pay but we don't generally say that, for this reason, wages make people act against their "better interests or judgement". Rather, we recognise that monetary gain must be counted as an important benefit to be weighed against the disbenefits of going to work (such as giving up one's free time). So I would recommend taking a similar approach to biomedical research and tissue donation.

Finally in Part 1, we need to look at the idea that financial incentives (above a certain level) can make people's decisions less autonomous. Again, the main idea is that certain sorts of payment, or payment in certain circumstances, exert 'undue influence on a participant's decision'.[13] It's no accident that accusations of undue inducement almost always occur in one of two different contexts. The first is where the 'victim' of the inducement is in desperate need of money due to poverty, or because she has some special need – such as to purchase costly medical treatment. The second is where the 'victim' isn't in desperate need of money, but is offered such a huge amount of money to do X that doing X becomes almost irresistible. Let's call these 'desperate offeree' cases and 'enormous offer' cases. One notable thing that they have in common is that there's a huge gap between the offeree's level of welfare if she doesn't accept the offer, and her level of welfare if she does accept the offer. In desperate offeree cases, this is because the offeree needs what's offered and will be substantially harmed if she doesn't get it, while in enormous offer cases, it's because of the offer's sheer size.[14]

For our purposes, the important question is: is valid consent possible in desperate offeree cases and enormous offer cases? We should certainly concede immediately that in both scenarios it will usually be tremendously hard for offerees to decline what's on offer. However, consideration of the following example (from Wilkinson & Moore) suggests that this isn't, in and of itself, a reason to think that autonomous and valid consent is impossible:

> If the sole alternative to death is some lifesaving treatment, then one is unfree to turn it down, but this does not rule out autonomous choice of the treatment. All the features of autonomous choice might be present: careful deliberation, correct understanding of the options, no manipulation, and so on. If informed consent is possible, despite the dire choice one faces, it cannot be because one is free to refuse the treatment. It must be because one can nonetheless act autonomously.[15]

So, as Wilkinson & Moore point out, even if we grant that there's a sense in which the recipients of enormous offers and desperate offerees aren't free to decline, this doesn't mean that they can't autonomously accept and validly consent. This must be so. Otherwise, it would be impossible for anyone ever to consent validly to lifesaving operations, not to mention lottery 'jackpot' wins or large salaries; the mere fact that a

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proposal is tremendously attractive clearly doesn't mean that it can't be validly and voluntarily accepted by the offeree.

Given this, the position as regards tissue is as follows. In many cases, the monetary rewards offered to tissue donors are relatively modest and the donors are not in any way 'desperate'. These cases are pretty unproblematic (in consent terms) provided that the other elements of valid consent (in particular, adequate information and competence) are in place. There may however be a few cases which fall into the desperate offeree and/or enormous offer categories outlined above: cases in which the prospective tissue providers are significantly economically disadvantaged and/or where the rewards are unusually large. In some of these cases, it may be legitimate to ask whether the consent is truly voluntary.[16] But, as the lifesaving treatment and similar examples show, valid consent is not only possible in such cases, it would appear to be the norm. So even in the 'worst case scenario' (where a large payment is offered to an impoverished research subject) it will usually be possible for the person to consent autonomously and voluntarily to selling her tissue. And so what was earlier labelled argument (c) would appear to be very weak.

In Part 1, we've reviewed a particular set of arguments against paying people for supplying tissue for research purposes. Each one of these is a version of the Inducement Argument and seeks to establish that monetary incentives should be avoided because they are likely to invalidate consent. For the reasons outlined above, we should conclude that these arguments are quite weak. This doesn't on its own count decisively in favour of permitting payment since there may well be other objections that are nothing to do with consent. But we have at least seen that the case against payment is not as strong as it at first appears, especially since (as Anderson and Weijer point out) consent and voluntariness objections are amongst those most commonly raised in the extant ethics literature:

> To the extent that the practice of paying research subjects for study participation has been examined in the literature to date, critical reflection has focused on questions related to the voluntariness of consent when subjects are paid, and the injustice of preferential enrolment of the poor in studies that pay subjects.[17]

They also mention 'the injustice of preferential enrolment of the poor' and this would be a fruitful area to explore in search of alternative objections to payment.[18] That said, my own view (argued for elsewhere) is that such arguments usually turn out to be unsuccessful, not (of course) because exploiting economically disadvantaged people is acceptable, but because they generally apply equally to a very wide range of commercial practices, not just against commerce in human tissue.[19] In other words, they fail to single out for especially restrictive treatment or condemnation the commodification of the human body, as opposed to commodification in general, which could include the whole of what is sometimes called 'capitalism'.

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[2] Commercial Exploitation By Third Parties

As Bauer, Taub and Parsi point out, the commercialisation of human tissue, or at least the commercialisation of research using human tissue, is potentially beneficial in a number of ways:

> For industry, the likelihood of profit based on medical products derived from human tissues is an effective incentive to invest in related academic research. With the judicious use of patents and other forms of intellectual property rights, industry has added reason to support cutting-edge and sometimes financially risky academic research involving human tissues. From the perspective of academic centers, the infusion of capital by industry can help to fund innovative research and support the training of researchers. Perhaps the most important benefit associated with the commercialization of human tissue comes from the successful interchange between the two spheres, toward a more efficient transmission of knowledge from academic based tissue banks to industry, facilitating the development and delivery of medical products to the public.[20]

This view is backed up by the MRC:

> The development of new drug therapies, and diagnostic and screening tests, to the point where they can be made sufficiently widely available to benefit human health, is crucially dependent on commercial involvement. Therefore access by the commercial sector to samples of human material collected in the course of MRC-funded research should be facilitated, where this is consistent with our mission.[21]

So there is a fairly strong prima facie case for (at least some forms of) commercialisation and, in this part of the paper, I ask whether there is anything morally wrong with third parties (e.g. academic researchers or biotechnology companies) commercially exploiting human tissue?

Human tissue can be commercially exploited in countless ways. Nonetheless, it is useful to draw a distinction between three main categories of commercial activity. First, and most straightforwardly, a researcher (or other tissue gatherer) could simply sell a physical tissue collection, or part of it, for profit. Second, tissue banks could sell services to researchers, such as limited access to a tissue collection, or the provision of data about a tissue collection. Finally, one might base intellectual property rights (including, but not just, 'DNA patenting') on research involving human tissue.

Applying to all of these categories is a further distinction between 'consent issues' and issues which (arguably) persist even when valid consent has been obtained. The most obvious consent issues arise when no consent for tissue donation has been obtained or, more commonly, when questions are raised about the information available to the donor at the time when she consented. In particular, was she aware, when she consented, that her tissue would be used for commercial purposes and, if not, ought she to have been made aware of this as part of the informed consent

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process? On this point, the GMC gives the following advice to doctors engaged in research:

> 14. You must be open and honest in all financial and commercial matters relating to your research and its funding. In particular you must: declare to research ethics committees, prior to the research being approved, all financial interests and sums of money which you know, or estimate, will be paid for the research undertaken; accept only those payments and benefits approved by the research ethics committee; give participants information on how the research is funded, including any benefits which will accrue to researchers and/or their departments; respond honestly and fully to participants' questions, including inquiries about direct payments made to you and any financial interests you have in the research project or its sponsoring organisations …
>
> 24. … Where material is being obtained for a specific project, you must explain how the sample will be used; where a sample is to be stored and used in further research projects, this must be made clear. You must be prepared to respond honestly and sensitively to any questions which the participants may ask.
>
> 25. You must be open and honest about any financial transactions associated with the use of tissues, organs or body fluids …[22]

This looks like a 'gold standard' approach as far as the financial interests of doctor-researchers are concerned. Research subjects and research ethics committees must be told pretty much everything about the uses to which donated tissue will be put and about the financial interests of researchers. However, the GMC guidelines don't (not least because of the GMC's particular remit) impose constraints on the behaviour of other organisations further 'downstream'. Hence, for example, a doctor-researcher might (with the consent of the research ethics committee and the research subject) pass tissue to a third party for only a modest payment covering 'administrative costs', only for that third party to use the tissue in a highly 'commercial' way later on.

> The MRC advises us that:
>
> Research participants may be particularly sensitive to the idea of a company or an individual making a profit out of research material that they have freely donated. It is important that research participants are made aware of the potential benefits of allowing commercial access, and that the role of any one individual's sample in the generation of future profits is likely to be minimal as well as impossible to quantify. Given the possible sensitivities, it is essential that research participants know that their sample or products derived from it may be used by the commercial sector, and that they will not be entitled to a share of any profits that might ensue.[23]

The GMC-MRC orthodoxy then is that tissue donors should, as part of the consent process, be told: (a) that access to their donated tissue by commercial organisations is possible or likely; (b) about the financial interests of the researchers; and (c) that they will not themselves get a share of any profits.[24] It does look then as if adhering to their standards will be sufficient to deal with most consent issues relating to

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commercialisation. For the basic idea, a simple one, is that if prospective tissues donors are warned in advance that commercial exploitation might take place (and that they don't stand to profit) then they can opt out and not give their tissue if they are unhappy with that arrangement. What is to be avoided above all else, since it would (as the MRC puts it) 'damage the gift relationship', is giving people false expectations about what will happen to their tissue.

Having made a distinction between 'consent issues' and issues which (arguably) persist even when valid consent has been obtained, I want to turn now to the latter, and to ask: assuming the presence of valid consent, is there anything wrong with a third party's commercially exploiting human tissue samples? Again, the GMC-MRC guidance is a good starting point. The GMC tells doctors that:

> Financial remuneration for supplying [tissues, organs or body fluids] to other organisations or individuals should be limited to administrative costs involved, and you should not be involved, directly or indirectly, in buying or selling human organs, tissues or body fluids.[25]

While the MRC tells its researchers that:

> The human body and its parts shall not, as such, give rise to financial gain. Researchers may not sell for a profit samples of human biological material that they have collected as part of MRC funded research … [but i]ntellectual property rights (IPR) arising from research using human samples may be sold or licensed in the same way as other IPR.[26]

The idea that 'the human body and its parts shall not, as such, give rise to financial gain' is a commonplace one and this form of words can be found in Article 21 of the Council of Europe's Oviedo Convention.[27] Clearly, the 'as such' is crucial for the MRC which (like many writers on this subject) posits an important ethical boundary between, on the one hand, selling body parts (as in, for example, the human kidney trade) and, on the other, owning and selling intellectual property in inventions which are based on human tissue research. In the remainder of this paper I review two arguments for this distinction.[28] The first says that while buying and selling physical human tissue involves (or is likely to involve) wrongfully treating human bodies as mere commodities or objects, this is not true (or is less likely to be true) of commercially exploiting inventions based on human tissue research. The second says that permitting researchers to have intellectual property rights in inventions based on human tissue research is a fair way of recognising and rewarding their creative endeavour, while this is not true of merely trading physical human tissue (which involves little or no creative endeavour).

The first argument relies on two premises: that we ought not to treat human body parts or tissues as mere objects or commodities (that we ought not to objectify or commodify them); and that buying and selling body parts or tissues would involve objectification and/or commodification.

The term 'objectification', when used in this debate, is almost always used as a negative moral concept. In other words, 'objectification' is taken to mean 'wrongful

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objectification'. But what particular kind of wrong is objectification? Not surprisingly, to objectify is to treat as a mere object. However, treating objects as objects doesn't count as objectification. Rather, to objectify is to treat as a (mere) object something which isn't really an object. As Nussbaum puts it:

> Treating things as objects is not objectification, since … objectification is making into a thing, treating *as* a thing, something that is not really a thing.[29]

Similar considerations apply to 'commodification'; to 'commodify' (in the moral sense) is to treat as a (mere) commodity something which isn't really a commodity (and so arguably we couldn't, in the moral sense, commodify baked beans or coal).[30]

When discussing objectification, and connected concepts such as commodification, it is always worth reminding ourselves of something which is obvious and yet sometimes overlooked in discussions of the commercialisation of the body: the fact that bodies and body parts are physical objects. Hence, any ethical concerns that we have about the objectification of bodies can't be about whether bodies are treated as objects, since they are objects. Rather, our concerns must be about whether bodies are treated as mere objects. So the crucial question is: what does 'mere' mean here? Or, to put it another way, what might bodies be over and above physical objects? What is treating a body as a mere object to be contrasted with? There seems only to be one remotely plausible answer to this. Bodies are more than mere objects insofar as they are somehow intimately related to persons.[31]

So to objectify the body is to treat it as a mere object and this means treating it as if it weren't intimately related to a person. But what is it to treat human tissue, or a human body, as if it isn't intimately related to a person? In practical terms, consent and harm will be vitally important. For two of the main ways of treating a human body as a mere object are: (a) doing something to it without requiring the person's valid consent, and (b) doing something to it which will harm the person. Indeed, while there isn't space to argue the point here, I would go further and suggest that the following moral principle is true: A does not objectify B by doing x to B's body provided that (i) A requires B's valid consent to do x and wouldn't do x without B's valid consent and (ii) x is not substantially harmful to B and A wouldn't do x to B if she believed it to be substantially harmful to B.[32]

This view of objectification has some direct implications for the issue at hand. In particular, what we are presently looking at is the question of whether there is anything wrong with a third party's commercially exploiting human tissue samples when valid consent is present? So we already know, ex hypothesi, that consent isn't a problem in the cases under consideration. This just leaves us with the harm issue: more specifically, the question of whether selling a donor's tissue for profit would harm her even in cases where she had consented. In answer to this we should certainly concede that harm is possible. For example, personal information about the donor could inadvertently be released in unfavourable circumstances, or the output of the research might harm society in ways that adversely impact on the donor. However, almost all of the foreseeable harms would seem to arise not because of

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commercialisation per se, but just because the research was carried out, or because tissue samples were transferred (whether for profit or not).

It seems therefore that the risk of wrongful objectification will be minimal in the cases under discussion because: (a) we already know, ex hypothesi, that consent isn't a problem, and (b) harm to the donor will be extremely unlikely and/or not caused by commercialisation per se. Of course, wrongful objectification is a very real prospect in cases where the GMC-MRC consent guidelines are not followed, but this is an argument for following the consent guidelines, not a wider anti-commercialisation argument.

Let's turn now to the second and final argument which, for reasons that will become clear in a moment, I'll call the Neo-Lockean Argument. This says that permitting researchers to have intellectual property rights in inventions based on human tissue research is a fair way of recognising and rewarding their creative endeavour, but this is not true of merely trading physical human tissue which involves little or no creative endeavour. An important distinction between tangible and intellectual property underlies the Neo-Lockean Argument.[33] For our present purposes, tangible property is physical human tissue, and this is to be contrasted with (for example) data sets concerning human tissue collections or patents on biotechnological inventions, both of which are intellectual property. With this distinction in place, the argument says that, although certain kinds of intellectual property in the human body are acceptable because they fairly reward researchers for their creative efforts, simply owning and trading body parts and tissues cannot be justified in this way, because these are natural resources.

Underlying this is the Locke's idea that property rights are justified principally by the extent to which someone's labour has been 'mixed' with a natural resource. Locke tells us that:

> Whatsoever then he removes out of the state that nature hath provided, and left it in, he hath mixed his labour with, and joined to it something that is his own, and thereby makes it his property. It being by him removed from the common state nature hath placed it in, it hath by this labour something annexed to it, that excludes the common right of other men: for this labour being the unquestionable property of the labourer, no man but he can have a right to what that is once joined to, at least where there is enough, and as good, left in common for others.[34]

According to the Neo-Lockean Argument, this entails that tangible property in human tissue isn't justified, since human tissue is a naturally occurring resource which is simply gathered by the researcher. There is no 'mixing' of labour and the resource, simply the appropriation of the resource. Intellectual property in biotechnological inventions however can be justified even when based on human tissue, because the researcher 'mixes her labour' with the tissue.

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This Neo-Lockean Argument though is problematic, chiefly because the distinction between cases in which tissue is merely appropriated and cases in which it is 'mixed with' the researcher's labour is not clear-cut. The most obvious difficulty is that even someone who just gathers and banks tissue is mixing her labour with it. Indeed, modern tissue gathering and banking, if it is to be done well, requires substantial effort, skill, and investment. So, even if we concede that tissue banking generally requires less labour than creating new biotechnological inventions, it is nonetheless clear that it requires some labour, often quite considerable amounts, and so it looks as if tissue bankers and gatherers will meet Locke's criterion for property rights. Tissue banking is (in some respects) akin to fishing and hunting and, as Locke himself points out, such activities generally involve labour in ways that justify property claims. In other words, fisherman and hunters are generally entitled to own and sell what they acquire, even though they didn't create or invent it, because of the labour involved in the harvesting process.[35]

At this point, it may be objected that an important difference between gathering human tissue and fishing is that, while human tissue is gifted by individual donors, fish are simply taken from a common stock (if we restrict ourselves to cases in which the fish and water are not privately owned, that is). So perhaps this, the fact that it is a gift, can account for the (alleged) wrongness of 'selling on' human tissue.

Certainly talk of 'gifting' and 'the gift relationship' is ubiquitous in ethical debates about the commodification of human tissue.[36] However, I doubt whether citing 'the gift relationship' will do much to help the Neo-Lockean Argument. This is, firstly, because banking gifted tissue doesn't require any less labour on the part of the banker than banking tissue acquired in other ways. Indeed, acquiring gifted tissue may well be more labour-intensive than the main alternatives because of the time spent obtaining informed consent from the donors. So the fact that tissue is 'gifted' doesn't seem to make much difference as far as the Neo-Lockean labour-criterion for property rights is concerned. Secondly, we should remember that the fact that someone gives a thing to someone else as a gift isn't, in and of itself, a reason for the recipient not to then sell that thing to a third party. Rather, the moral status of 'selling on' depends on specific features of the original giving. In particular, did the original gift come with the giver's consent for onward sale, did it come with any conditions or 'strings' attached, and would 'selling on' hurt the giver's feelings? We cannot infer from the bare fact that something is a gift that it cannot be sold on, and there are lots of gift situations in which it is understood from the outset that 'selling on' will take place: for example, when people give their clothes to charity shops for resale, or donate their empty bottles to commercial companies for recycling. There's no reason why tissue donation can't be modelled on these, generally rather benign, practices. 'Selling on' gifts may of course be objectionable when the giver doesn't expect it and is hurt or offended by it (for example, if I were to sell off all my birthday presents, my friends and relatives might, with some justification, take offence and think that I had acted badly). But, as we saw earlier, this kind of issue can really be dealt with by having adequate informed consent procedures at the outset and by following the GMC-MRC guidelines (or something similar). In particular, as the MRC puts it: 'it is essential that research participants know that their sample or products derived from it may be used by the commercial sector'.[37]

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Finally it is worth noting that, even if the above criticisms of the Neo-Lockean Argument are unsound, the argument still might not support a very clear-cut moral distinction between intellectual and tangible property. This is because certain forms of intellectual property, in particular those 'DNA patents' which are very closely related to naturally occurring substances, might themselves be legitimate targets for the Neo-Lockean Argument. For, it has been argued, some such patents merely appropriate what already exists in nature in the same way that physical tissue gatherers (allegedly) do. Indeed, DNA patent holders, it could be argued, fall foul of Neo-Lockean principles to an even greater extent than physical tissue gatherers, since the former not only collect but also try to monopolise natural resources and to stop others from using them via patent rights. Clearly, there is much more to be said about the whole subject of 'DNA patenting'. Nonetheless, it is worth keeping in mind that intellectual property based on human tissue research is itself a controversial and difficult topic, quite possibly more so than the ownership and sale of physical tissue.[38]

Conclusions

In Part 1, we saw that the case against paying research subjects for their tissue is not as strong as it at first appears. In Part 2, we moved on to look at third party commercial exploitation of human tissue by (for example) researchers, tissue banks, and biotechnology companies. Two main conclusions emerged. Firstly, there was broad support for the 'orthodox' view of informed consent expressed by, amongst others, the GMC and MRC. Roughly, this says that prospective tissue donors should be given very full information about the extent to which their tissue will be commercially exploited and about the financial interests of the tissue gatherer/researcher. Secondly, some scepticism was expressed about another widely held view: the idea that while 'the human body and its parts shall not, as such, give rise to financial gain', intellectual property based on human tissue research is generally acceptable.[39] It was argued that some of the main ethical objections to owning and trading physical human tissue are unconvincing and/or that they apply equally to tangible and intellectual property. None of this counts decisively in favour of permitting the widespread commercialisation of human tissue, but (as with Part 1) we have seen that the 'anti–commercialisation' arguments are perhaps not as strong as they at first appear.

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[1] Council of Europe. 1997. Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine (CETS 64).
[2] K Bauer, S. Taub, & K. Parsi. Ethical Issues in Tissue Banking for Research: a brief overview of existing organization policies. Theoretical Medicine 2004; 25; 113–142 [p. 128]
[3] M. Lock. The Alienation of Body Tissue and the Biopolitics of Immortalized Cell Lines. Body & Society 2001; *7;* 63–91 [p.65]
[4] Like Wilkinson & Moore, I prefer the term 'subjects' to 'participants' The latter term is ambiguous between researchers and research subjects. Furthermore, only some kinds of research require the subjects' participation. M. Wilkinson & A. Moore. Inducement in Research. Bioethics 1997; 11; 373-389. [p.373]
[5] MRC (Medical Research Council). 2001. Human Tissue and Biological Samples for Use in Research: 3.
[6] Nuffield Council on Bioethics 1995. Human Tissue: ethical and legal issues: vi.
[7] R. Faden & T. Beauchamp. 1994. The Concept of Informed Consent In Contemporary Issues in Bioethics. T. Beauchamp & L. Walters, eds. Belmont, CA: 149. R. Gillon. 1986. Philosophical

Medical Ethics. Chichester. Wiley: 113. S. Wilkinson. 2003. Bodies for Sale. London. Routledge: 76.
[8] Nuffield Council on Bioethics. 2002. The Ethics of Research Related to Healthcare in Developing Countries: 76.
[9] Another related reason, not discussed here due to lack of space, is that some offers of monetary reward can be coercive. For a full discussion of this argument see: S.Wilkinson, op. cit. 6, pp. 82-98 & 116-129.
[10] GMC (General Medical Council). 2002. Research: the role and responsibilities of doctors: s.14.
[11] See: Nuffield Council on Bioethics, op. cit 7, pp. 78-9.
[12] For an interesting illustration of this problem see: R. Boyd. A view from the man in the seat opposite. BMJ 1998; 317; 410.
[13] Nuffield Council on Bioethics, op. cit 7, p.14.
[14] S.Wilkinson, op. cit. 6, pp. 116-26.
[15] Wilkinson & Moore, op. cit 3, p. 377.
[16] Distinguishing between those cases in which there's a 'voluntariness problem' and those in which there's not will however be difficult. S.Wilkinson, op. cit. 6, pp. 75-97, 105, & 116-26.
[17] J. Anderson & C. Weijer. The Research Subject as Wage Earner. Theoretical Medicine 2002; 23; 359–376. [p.359]
[18] See: Nuffield Council on Bioethics, op. cit 7. S.Wilkinson, op. cit. 6, pp. 9-26 & 130-2.
[19] B. Brecher. The Kidney Trade: Or, the Customer Is Always Wrong. Journal of Medical Ethics 1990; 16; 120-123. Brecher, B. Organs for Transplant: Donation or Payment? In R. Gillon, ed. Chichester. John Wiley & Sons: 993–1002. S. Wilkinson & E Garrard. Bodily Integrity and the Sale of Human Organs. Journal of Medical Ethics 1996; 22; 334-339. S. Wilkinson. The exploitation argument against commercial surrogacy. Bioethics 2003; 17; 169-187. S.Wilkinson, op. cit. 6.
[20] Bauer et al, op. cit 1, p. 114.
[21] MRC, op. cit, 4, p. 12.
[22] GMC, op. cit 9.
[23] MRC, op. cit, 4, p. 12.
[24] The question of whether donors should get a share of any profits is another interesting issue that can't be discussed here owing to lack of pace.
[25] GMC, op. cit 9, s.25.
[26] MRC, op. cit, 4, p. 3.
[27] Council of Europe. 1997. Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine (CETS 64). It should be noted that the UK is not a signatory to this treaty.
[28] A further argument for this distinction, which there isn't space to review here, says that permitting researchers to have intellectual property rights in inventions based on human tissue research will have generally beneficial effects by incentivising research and development, whereas this is <u>not</u> true of allowing the trading of the physical tissue itself. For further discussion of this complex empirical issue see for example: M. Heller and R. Eisenberg. Can Patents Deter Innovations? The anti-commons in biomedical research. Science 1998; 280; 698-701. D. Resnik. DNA Patents and Scientific Discovery and Innovation: assessing benefits and risks. Science and Engineering Ethics 2001; 7; 29-62. S.Wilkinson, op. cit. 6, pp. 199-206.
[29] M. Nussbaum. Objectification. Philosophy and Public Affairs 1995; 24; 249-291. [p. 257]
[30] S. Wilkinson. Commodification Arguments for the Legal Prohibition of Organ Sale. Health Care Analysis 2000; 8; 189-201. S.Wilkinson, op. cit. 6, pp. 27-55.
[31] The expression 'somehow intimately related to persons' is meant to be metaphysically innocent and is not meant to imply any form of dualism, since one of the <u>possible</u> relations between persons and their bodies is identity.
[32] This is a rather cautious formulation of a principle that provides sufficient conditions for non-objectification. It may be that less cautious versions are also true (e.g. perhaps requiring valid consent is enough for non-objectification). If they are, then this will provide further support for the argument advanced here. See: S.Wilkinson, op. cit. 6, pp. 27-55 & 72-81.
[33] For further explanation of this distinction see: S.Wilkinson, op. cit. 6, pp. 183-7.
[34] J. Locke. 1690. Second Treatise of Government: s. 27-8.
[35] Ibid.

[36] The work standardly cited in connection with this point is R. Titmuss. 1970. The gift relationship: from human blood to social policy. London. Allen and Unwin.
[37]MRC, op. cit, 4, p. 12.
[38] For further discussion see: L. Andrews and D. Nelkin. 2001. Body Bazaar: the market for human tissue. New York. Crown. Nuffield Council on Bioethics. 2002. The Ethics of Patenting DNA: a discussion paper. D. Resnik. The Morality of Human Gene Patents. Kennedy Institute of Ethics Journal 1997; 7; 43-61. S. Wilkinson. Intellectual Property Rights and the Human Body: is 'gene patenting' a special case?. Imprints 2001; 5; 132-160. S.Wilkinson, op. cit. 6, pp. 83-245.
[39] Council of Europe, op. cit. 26.

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Human Tissue and Global Ethics

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Abstract

One important sense of 'global ethics' concerns the applied ethical issues arising in the context of economic globalisation. This article contends that we are beginning to witness the economic commodification and, concomitantly, the globalisation, of human tissue and the human genome. Policy-makers and local research ethics committees need to be aware that the relevant ethical questions are no longer confined to their old national or subnational context. A shift from questions of personal autonomy and identity can therefore be expected—towards the more problematic issues of justice, exploitation and distribution. Here we can learn from the distinctions drawn in legal philosophy, such as the notion of property as a 'bundle' of rights, from which we may choose rights favouring the interests of vulnerable populations. We may also wish to apply the distinctions drawn by Calabresi and Melamed between pure property rules, modified alienability rules, and pure non-property regimes. Global ethics also concerns issues of value disparity across cultures, directing our attention to the moral beliefs of indigenous peoples, for example, whose DNA or tissue is increasingly of commercial importance. In examining case examples from Tonga and Aotearoa/New Zealand, I will consider the impact of indigenous belief systems and of neo-colonialism on indigenous peoples' perceptions of Western researchers. It is clear that many indigenous peoples reject both the pure property system and any modifications, insisting on a pure non-property regime. How can they then be protected in a globalised market system that so far favours the opposite end of the spectrum?

I. Commodification and globalisation

In July 2004 it was reported that the UK's Human Fertilisation and Embryology Authority was to visit a Bucharest clinic, in order to monitor the purchase of human ova from Romanian women by British clinicians. Although it was not suggested that the HFEA was brokering the transactions, many observers were shocked that the HFEA tacitly approved this commodification and globalisation of tissue, in the form of the cross-border trade in ova.[1] I was not so shocked, having predicted such developments in several articles and at a workshop on reproductive ethics issues involving women in the accession countries.[2] If this sounds like bragging, I hasten to say that I would much rather have been proved wrong.

My Delphic powers are minimal, and I never win at Bingo. But from Dolly's earliest days, as the sole survivor of 267 embryos each developed from genetic material injected into an enucleated egg, it should have been clear that the stem cell

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technologies would require large numbers of enucleated ova, that most IVF clinics in Western Europe were already short of ovum donors, and that commercial incentives to 'donate' would be particular irresistible to poor women in Eastern Europe or the developing countries. While the majority of commentators appeared most concerned with the moral status of the embryo, for embryonic stem cell technologies, or with the autonomy and identity of a clone, in reproductive cloning, I found myself more and more convinced that the real issues concerned the possibility of a global trade in ova, with the attendant questions of what was to count as commodification and exploitation if that trade did emerge.

For me the issues that counted, and that still count, were less to do with the classic concentration of bioethics on autonomy, informed consent and other such individual questions, and more to do with structural and societal issues concerning economic and political justice. It seems to me that the commodification and globalisation of human tissue and the human genome will catch bioethicists and social policy analysts unawares, unless they shift their gaze outward to global justice. Policy-makers and local research ethics committees need to be aware that the relevant ethical questions are no longer confined to their old national or subnational context. A shift from questions of personal autonomy and identity can therefore be expected—towards the more problematic issues of justice, exploitation and distribution.

This is of course an oversimplification: despite the unfavourable press they have recently had from some social scientists,[3] many bioethicists are fully aware of wider social questions of justice, which is after all one of the 'four principles'--even if a somewhat junior partner in the firm. Some of these international justice issues had already arisen, and continue to be debated, in the more widely discussed context of organ sale.[4] There, and more recently in examples drawn from genetics,[5] they have given rise to a debate on whether property in the body is a useful or even an accurate concept, and to proposed distinctions between sale, gift and other forms of exchange, which I shall examine in the next section. Ownership rights construed as forms of control, protecting individuals' autonomy, differ from rights seen primarily in terms of income, and some commentators rely on the first form of property rights to protect against injustice, while prohibiting or strictly regulating the second.[6]

Other commentators have rightly drawn attention to the global inequities that may arise between rich and poor nations and their nationals; what the ova sale example adds is whether there is also a question of gender injustice at a global level. We may be witnessing the creation of a new subject of global bioethics, now taught in at least one university[7], and centring on issues such as property in tissue, patenting, 'reproductive tourism', and other questions of global distribution. None the less, the combination of globalisation and commodification of human tissue more generally raises enormous and largely unaccustomed issues for bioethics and bio-law.

It might be well to begin by trying to define some terms, in order to get some purchase on this vastness. By the commodification of tissue, I mean the process by which tissue acquires value such that it becomes the object of exchange: not

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necessarily totally purely free market exchange, however. We can see in the HFEA example that a UK regulatory body empowered to licence IVF clinics, and to retract their licences, is attempting to regulate untrammelled exchange. In some senses this attitude is preferable to turning a blind eye; in other ways it represents accommodation with the inevitability of commodification. For those to whom commodification makes people and/or their tissue in some way into objects—and 'in what way' needs further unpacking, as I have attempted to do elsewhere[8] -- clearly this is neither desirable nor, in the last analysis, inevitable, since so long as people remain people rather than objects, they retain the possibility of agency, of doing something to prevent their own commodification.

In denying that commodification necessarily equates the free market exchange of practically everything, I follow Margaret Radin's warning: 'universal commodification is oversimplified, a caricature.'[9] It is neither accurate nor heartening to assume that simply because elements of tissue commodification have crept into medical research and clinical practice, we must accept the inevitability of full-blooded free markets in tissue. On the other hand, my definition in terms of exchange would include 'egg-sharing' and other practices in which money does not actually change hands, but the primary motivation is economic and the exchange mutual. It would not include blood donation, where in the UK, at least, there is no mutual exchange, except possibly tea and biscuits for the donor.

This will do for a working definition of what may be an unfamiliar concept to some, commodification—even though it has been said that 'in the last couple of decades, *commodification* has become almost a buzz-word in bioethics'[10]. Turning now to globalisation, definitions are no less sticky. I want to use the term neither in its vague and beneficent sense of 'growing interconnectedness and interdependence on a world scale,'[11] nor necessarily and exclusively in the malevolent characterisation of the anti-globalisation movement. Instead I want to present globalisation, in its economic guise, as the process by which capitalism penetrates global markets and audiences with minimal regulation. 'That meaning of globalization is associated first with the internationalizing of production by multinational corporations (MNCs) and then with the establishment of unregulated global financial markets.'[12] The global 'Gold Rush' in biotechnology is a prime example of the penetration of capitalism into previously non-capitalist relationships and societies; in section three I shall use the case example of Tonga to illustrate this claim.

II. Should human tissue be commodified?

If human tissue is to be commodified, it must in some sense be an object of property-holding. This is true even if the 'return' for the tissue is not monetary. In a broad sense, the question of commodification assumes that the prior question 'Can human tissue be an object of property?' has been answered in the affirmative.

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Some commentators—on both sides of the commodification and globalisation debates-- tend to assume that once the affirmative answer has been given, no further regulation is possible or desirable. That position is patently false: we regulate all kinds of property-holding. There are stringent limitations on my right to attack you with my kitchen knife, no matter how clear it may be that it is my legitimate property. Property is normally conceived in jurisprudence as a bundle of rights,[13] some of which may be partial or non-existent. I may have the right to sell my knife, or give it away, or gamble it in a game of mumblety-peg, but I do not have unmitigated rights over all of its uses merely because I am its owner.

What kinds of rights might I then have? In jurisprudence property is further conceived not as a single entity but as a 'bundle' of relationships, from which 'sticks' can be chosen at will by lawmakers, regulators and policy-makers.[14] One might, for example, wish to assure research subjects the 'stick' of protection against unauthorised taking, while not allowing them the 'stick' of profiting from long-term developments performed with their tissue.[15] In other words, property is not all-or-nothing, although liberal political theory tends to see it as such.

As John Christman says, '[T]he picture of ownership that history paints…is much more complex, murky and varied than defenders of the liberal paradigm of ownership might have us suppose.'[16] Christman denies that historically, the notion of property has ever involved full and absolute rights, without any restriction or regulation: this is not the natural state on which government then imposes, as in the liberal view of the social contract and in the Roman conception of 'sole despotic dominion'. Yet researchers, pharmaceutical firms and, yes, British IVF clinics are still widely assumed to enjoy undifferentiated and total power over the tissue they acquire.[17] Whereas in law the notion of property is so differentiated that some commentators deny there is such a thing as property at all,[18] in bioethics the 'all or nothing' model seems to be assumed by both proponents and opponents of property in tissue.

Bearing this *caveat* in mind has the effect of reducing some fears about the commodification of tissue. Even if tissue such as ova, or DNA, or blood, or organs, is commodified to the extent that it can be alienated from its original 'owner'[19]—and I use the scare quotes deliberately—that does not mean that we are powerless to regulate the means by which it can be transferred. It is not all or nothing: complete market commodification or total non-commodification. We may wish to allow the gift of blood, for example, but not its sale. The argument used by many 'pro-commodification' advocates, to the effect that it would be contradictory not to allow sale when we already allow gift, betrays an ignorance of legal philosophy.

Over thirty years ago, Calabresi and Melamed[20] distinguished between pure property rules (in which both gift and sale are permitted); liability or market-inalienability rules (allowing gift but not sale) and pure inalienability (forbidding both gift and sale). A pure property regime would prohibit all 'border crossings' (between the 'owner' and other parties) unless prior permission is granted, and compensation is paid at a rate determined by the property owner. Liability or market-inalienability rules allow such

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crossings or transfers without prior permission, but require compensation to be paid *ex poste*, at a rate to be determined by the state. Complete inalienability rules prohibit the transfer of the property object entirely, regardless of offers of compensation. (If the last category is the most unfamiliar, think of the analogy of the vote, which may be neither given away nor sold.)

Applied to human tissue in the global context, this analysis would yield three very different policy prescriptions. What we risk seeing in examples such as the Romanian one is an unregulated pure property regime, in which compensation is paid at a rate determined where the tissue 'owner' is either in a weak bargaining position, due to her comparative poverty, or not even consulted about the bargain at all. (For example, there have been reports of unauthorised taking of ova by Croatian gynaecologists, presumably for subsequent sale to Western European or US researchers and clinicians.) We could counter that risk by insisting that ova should not be alienable from their 'owners' in any circumstances, regardless of whether or not women are paid a great deal, very little, or anything at all. For policy reasons—such as difficulty of regulation, or awkwardness of setting a 'fair' price—or for reasons of core values—such as the symbolic importance of a legal ban in upholding human dignity[21]—we could decide that tissue should be totally inalienable at global level. (We might still believe that national jurisdictions should allow other property regimes within their own borders, where there might not be such huge disparities of wealth as between developing and developed countries; or we might not.)

Alternatively, we could choose the middle route: allowing tissue such as ova to be transferred, but at a rate to be determined by the state or some other form of allegedly impartial institution. Charlotte Harrison,[22] for example, has proposed a hybrid approach between the two extremes of total market freedoms to sell, trade or profit from property in human tissue, and a comprehensive ban on any form of tissue transfer, including gift. Harrison favours a modified alienability scheme whereby donors would be compensated by an objective administrative mechanism rather than by a market in tissue. This hybrid approach retains a general rule of donation for research tissue when acquired, but a non-market mechanism for compensation in those cases where donations later prove to have commercial uses. Harrison denies that commodification is necessarily entailed by this liability or market inalienability approach, whereby research users remain liable to compensate donors for tissue that proves valuable in further research developments. Rather, she argues, commodification is inextricably entangled with market mechanisms; compensation, if determined by a public body, actually avoids the worst evils of commodification.

To some Western observers[23]this modified alienability scheme represents an attractive compromise between a raging market in tissue and an impractical ban on all tissue transfer. If such a compromise could be engineered on a global level, some might feel, indigenous populations in the Third World would also enjoy better protections. The difficulty is that those populations themselves almost universally insist on total non-commodification—the third of Calabresi and Melamed's three views. Many indigenous peoples distrust the entire idea of giving informed consent to the use of

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human materials in commercial applications. From the Karioca Declaration at the Rio de Janeiro Environment and Development Summit onwards, indigenous peoples have widely rejected the notion that they can give any such thing as informed consent to what they view as a deeply wrong enterprise, the objectification and commodification of human life. Some of the reasons for this attitude are historical: an entirely understandable reaction to the excesses of colonialism, to the exploitation of colonial countries' resources and even the plundering of aboriginal corpses for Western museum collections.[24] In the recent example of Tonga, these attitudes resulted in a collapse of the negotiations with an Australian biotechnology company, with losses for both sides. The gulf between Tongan and Western values illustrated in this case highlights a second sense of global ethics: conflicts between competing value frameworks despite the appearance of value uniformity that globalisation has often been said to produce.

III. The Tongan and Maori cases

In November 2000 the Australian firm Autogen announced to the Australian media an agreement with the Tongan Ministry of Health, to collect tissue samples for the purpose of genomic research into the causes of diabetes—well-known for its high incidence, about 14%, among the Tongan population.[25] As the press announcement declared, the firm was attracted to the 'unique population resources of the Kingdom of Tonga.' Such relatively homogeneous indigenous populations are likely to possess an increasing appeal not only in terms of research into the genetic basis of such conditions as diabetes, but also for pharmacogenetic research, which is still in the early days of learning how to tailor drug regimes on a genomic basis. Randomised clinical trials testing the effects of pharmacogenetic drug regimes may well be cheaper to run on populations possessing a high degree of genetic similarity in both the experimental and control arms, since the required level of statistical significance will probably be available from smaller populations.

Although the Tongan public had not been informed of the initiative before the announcement in the Australian press, Autogen might have expected little resistance. It was offering several sorts of benefits: annual research funding for the Tongan Ministry of Health, royalties to the Tongan government from any commercially successful discoveries, and provision of drugs from such discoveries free of charge to the people of Tonga. However, although the Director of the Tonga Human Rights and Democracy Movement, Lopeti Senituli, had advocated similar benefits for indigenous peoples in a previous instance, when Smith Kline Beecham was pondering a bioprospecting agreement for *plant* samples in Fiji, he was wholly opposed to the Tongan government's agreement with Autogen concerning *human* tissue, despite its apparently lucrative benefits. As Senituli put it,

> *Existing intellectual property right laws favor those with the technology, the expertise and the capital. All we have is the raw material—our blood. We should not sell our children's blood so cheaply.*[26]

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It would be easy to dismiss this statement as a political war cry of dubious scientific accuracy. Of course the Tongans were literally not being asked to sell their children's blood. The DNA samples to be taken were renewable tissue in any case, and there was no theft of any individual's genome. But to dismiss Senituli's position so lightly would be an error, and a neo-colonialist one at that. It represents an appeal to an alternative and conflicting set of values, to which the second aspect of global ethics should alert us.

The Tongans' primary stated objection to the Autogen proposal was that only individual informed consent was to be sought, in accordance with the dominant ethical model in genetic databanks. 'The Tongan family, the bedrock of Tongan society, would have no say, even though the genetic material donated by individual members would reflect the family's genetic make-up.'[27] They also had highly pragmatic objections: for example, they cannily surmised that Autogen would reap rewards, such as higher share values and provision of venture capital from the pharmaceutical industry, as soon as the agreement was announced--whether or not any therapies were eventually developed. By contrast, 'the promised royalties from any therapeutics and the provision of those therapeutics free of charge to the Tongan people were, we felt, prefaced by a huge "IF".'[28] In the face of this opposition, Autogen quietly dropped its proposed Tongan DNA databank in 2002, announcing that it would conduct its research in Tasmania instead but then disappearing from view altogether.

If the issue of extended consent could have been solved, and if the benefits of the agreement had been made more secure, would the Tongan opposition have been placated? Senituli says no: ultimately the conflict with Tongan values was simply too great, and the threat from global commodification too vast.

> *The Tongan people in general still find it inconceivable that some person or Company or Government can own property rights over a human person's body or parts thereof. We speak of the human person as having "ngeia", which means "awe-inspiring, inspiring fear or wonder by its size or magnificence.' It also means 'dignity'. When we speak of "ngeia 'o te tangata" we are referring to 'the dignity of the human person' derived from the Creator…Therefore the human person should not be treated as a commodity, as something that can be exchanged for another, but always as a gift from the Creator.*[29]

Again, to dismiss these objections as biologically incorrect—because no individual human being is owned or exchanged as a commodity by a DNA databank—is to miss the point. Global ethics in its second sense reminds us of the need to understand explanations such as this in their wider cultural context. Just as improved benefits or community consent would not have been sufficient counterweight to the Tongans' core objections, so correction of 'misperceptions' about the science involved would be insufficient to balance the power of a host of core ethical beliefs in Polynesian cultures. In the closely related Maori culture of Aotearoa/New Zealand, the concept of

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human dignity to which Senituli refers is linked to the core values of *mana tipuna,* prestige and authority drawn from the ancestors; *tapu o te tangata*, the sanctity of the person; *whakapapa*, genealogy; and *mauri*, or life force. (The Maori language also uses the word *ira* for the life principle; it is also the closest Maori translation to the word 'gene'.[30])

As the eminent Maori cultural studies professor Hirini Moko Mead has written, Maori culture views one's personal *tapu* as the most important spiritual attribute of the individual.[31] 'This attribute is inherited from the Maori parent and comes with the genes.' The aim of a good life is to preserve and enhance *tapu*, keeping the self in a steady state of balance. Actions by self or others that take away *tapu* are to be avoided. In the Polynesian context, it might well be thought that allowing others to take away one's genetic material is a violation of *tapu*, resulting in a diminution of the *tapu* available to one's descendants and affronting one's ancestors, who have striven to preserve their own *tapu* as a legacy. The ultimate source of *tapu* is seen as the primeval parent gods and their divine children, and the greatest threat to the vitality of the entire Maori people, embodied in this legacy from the earliest parents, is perceived by Maori elders as the assaults of European *pakeha* culture on Maori customs. An earlier anthropological study (Best, 1941) recorded the powerful statement from one elder 'that the vitality of their race departed with the loss of *tapu*, leaving the people in a defenceless and helpless condition.'[32]

Although learning for its own sake is highly esteemed in Polynesian cultures, research for principally financial gain does not necessarily share the same high value. On the other hand, if it could be known definitely that the proposed research might have lowered the high Tongan rate of diabetes or provided more effective therapies, the value of *tapu* might be displaced from its usual pre-eminent position. The countervailing value of *mauri* or life force could arguably be enhanced, one might think. However, Maori and Polynesian values in general are by no means utilitarian. Even if the benefit to be derived from the research were definite, there would still be qualms about sacrificing even a small part of some individuals' life force in order to benefit others.

Mead discusses a similar reluctance in the instance of xenotransplants. Although it might be thought that Maori values would allow the implantation of a pig's heart valve, for example, in order to save a human, Mead is in fact unwilling to allow this sacrifice as unproblematic in terms of *mauri,* which pigs too possess. It is the offence against *mauri* as a life-force which renders a consequentialist balancing of harms inapplicable—or, to translate into the utilitarian calculus, which requires us to set a value on *mauri* in the abstract, as an ultimate value to be maximised, regardless of where and how it is embodied. In the case of xenotransplantation, Mead argues:

> *In the final analysis a mauri is sacrificed to save another and this is not an ideal situation. The rationalisation for sacrificing the pig is that we kill it and eat it anyway. But when we eat it we do not call it pig, but rather pork. Eating pork, however, is quite different from using living tissues of a pig to keep us alive…Many*

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> *of us have qualms about employing living pig tissues to repair damaged human parts. Why is this? In the case of pork the pig is killed, prepared, cooked and eaten by us. The mauri of the pig is extinguished in the process…In contrast, living tissue used to repair human parts continues to live…Part of the mauri of pigs remain [sic] in human beings as living tissue…We doubt that the mauri and tapu of the pig are in fact completely extinguished, and this is a concern.*[33]

In the case of DNA samples taken for the proposed Tongan research on diabetes, there is no cross-species violation of *mauri*; no research subjects are asked to sacrifice their *mauri* for the greater good of the community, or Autogen. I have already suggested, however, that they are being asked to infringe their personal *tapu*, and that a countervailing claim that *mauri* will instead be enhanced for the community as a whole would not be unproblematic. In other instances in bioethics where a Western analyst might employ a consequentialist, balancing mode of reasoning, such as xenotransplants, a Maori analyst is loath to let the benefit to some outweigh harm to the life force in other persons or indeed any other creatures.

The subtle analysis suggested by Mead distinguishes between certain permissible uses of pigs, including eating pork, because *mauri* has already been extinguished in the pigs and can be enhanced in the humans who use pork as sustenance. In the case of genetic material, however, it is living tissue that is being taken, so that *mauri* is not extinguished. Not only is the taking of such tissue wrong in terms of both *tapu* and *mauri*; even the beneficial employment of Tongan DNA to produce more effective therapies for the Tongan population might be suspect, to the extent that living cell lines are involved. For example, an immortal cell line such as that produced through stem cell therapies would continue to contain the *mauri* of the individual who donated the genetic material, as well as the *mauri* of the woman who donated the enucleated ovum. The mixing of these individuals' *mauri* with that of the recipient patients might be ethically problematic, even if the *mauri* of the recipient were enhanced.

Maori and other Polynesian values might appear to forbid any 'border crossings', to return to the terminology of property, liability and inalienability. However, there are also aspects of Maori culture concerned with repairing breaches of *tapu* and *mauri,* in effect compensating for border crossings once they have occurred, more in the manner of liability. In the *take* procedure, the starting point for repairing such breaches is to acknowledge that they have occurred and that a wrong has been committed. Had Autogen acknowledged that harm had been done to Tongan values, regardless of the benefits offered, the resultant breakdown of negotiations might not have occurred.

Possibly this seems an impossibly high price to exact of a Western company, particularly because the Polynesian sense of harm does not accept the Kantian excuse of good intentions. 'All offences appear to be offences of strict liability.'[34] It would not be sufficient for Autogen to claim that they intended no harm; once core values such as *ngeia* had been offended, harm had occurred. However, the subsequent process of *utu* or reparation does provide a blueprint for negotiation, in the hope of establishing *ea* or balance between the conflicting viewpoints. Complete value

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relativism is neither necessary nor desirable: accommodation between indigenous and Western values can in principle be reached, through recognition of the validity of indigenous frameworks. The Bioethics Council of New Zealand has recently completed a consultative exercise on the use of human genes in other organisms, for example, in which both Maori and *pakeha* values were canvassed—although some Maori critics viewed this exercise as more top-down than bottom-up.[35]

As Mead notes, 'the debates are likely to be contested, and since we are now dealing with global rather than local issues, with believers and non-believers, and with Maori and non-Maori, it is much more difficult to reach agreement.'[36] This pessimism about the possibility of reaching accord between 'indigenous' and Western values is borne out by the Tongan case, and in New Zealand by the rather formulaic hearing given to Maori beliefs during hearings by the Environmental Risk Management Authority over an application by the 'Dolly' firm, PPL Therapeutics, to field-test transgenic sheep in order to produce a cystic fibrosis treatment, human alpha-I-antitrypsin. Taking the position advanced by the Ngati Raukawa tribe's response to the consultation, the Maori advisors to the ERMA recommended that the application should be denied, representing as it did an unacceptable transgression against sacred values. However, the ERMA allowed the application after a 'balancing' test, holding that Maori cultural objections were outweighed by the possibility of relieving cystic fibrosis—which, it should be noted, disproportionately affects those of European descent. We have also seen that Maori values do not admit of this sort of utilitarian balancing; it is therefore rather mystifying that the ERMA denied that it had dismissed Maori objections, and that the risks to Maori culture had been adequately considered.[37]

It is also a neo-colonialist error, however, to draw an overly black-and-white picture of the differences between indigenous and Western beliefs, or indeed to categorise those beliefs too rigidly into the very categories 'indigenous' and 'Western'. For patients and donors in the First World, human tissue has also been found in ethnographic surveys to retain elements of 'life-force', or of personhood and identity.[38] A Quaker response to the New Zealand transgenic consultation exercise rejected the insertion of human genes in other organisms on grounds that independently echoed Maori beliefs, presenting the gene pool as a collective legacy for which we owe a collective responsibility.[39] Feminist theory may be particularly alert to the complex effects inherent in embodied identity.[40] Here, too, global ethics in its second sense should warn us against too automatic an assumption of cultural relativism, and assist us in tracing the common elements between cultures. Global bioethics as a progressive movement has widened the issues considered by bioethics and the perspectives it employs.[41]

Acknowledgements

My little knowledge of Maori ethics was gained from the kind invitation from Nga Pae o te Maramatanga, the National Institute for Research Excellence in Maori Development and Advancement in Aotearoa/New Zealand, to speak at a conference on 'Research ethics, tikanga Maori/indigenous and protocols for working with

communities,' held in Wellington on 10th-12th June 2004. I am very grateful to Lopeti Senituli for presenting me with a copy of his paper at this conference and for his helpful answers to my questions. My thanks also to Mera Penehira, Paul Reynolds and Sharon Hawke for looking after me so well during this conference, and to Professor Linda Smith for providing comments on a draft version of this paper. John Pennington, Executive Officer of Toi Te Taiao/The Bioethics Council, was hospitable and helpful in providing me with materials and explanations concerning the human gene transplantation consultation exercise.

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[1] (Core) Comment on Reproductive Ethics, (Corethics.org. website, visited 22.7.2004, quoting a report in the *Sunday Times* that the visit had taken place on 15th July. 'That the HFEA thinks it appropriate to lend its support to such practice, and in an overseas country, is beyond belief…That they can imagine it is their duty to police clinics in Europe, particularly in the poorer countries where the potential for exploitation of vulnerable women is immense, is truly shocking. Egg harvesting can be a life-threatening intervention for the women involved, and at the very least the HFEA should remain absolutely neutral on this issue, not promoting it in any way.' (Statement from Core director Josephine Quintavalle)

[2] D.L. Dickenson. Property and women's alienation from their own reproductive labour. Bioethics 2001; 15; 205-217; D.L. Dickenson. Commodification of human tissue: implications for feminist and development ethics. Developing World Bioethics 2002; 2; 55-63; D.L. Dickenson. Consent, commodification and benefit-sharing in genetic research. Developing World Bioethics 2004; 4; D.L. Dickenson. Reproductive rights and property in the body. Paper delivered at the San Sebastian workshop of the Network for European Women's Rights, February 2004.

[3] For example, A.M. Hedgcoe. Critical Bioethics: Beyond the Social Science Critique of Applied Ethics. Bioethics 2004; 18; 120-143.

[4] E.g. Calabresi, Wilkinson, Murray, Shannon, T. Harrison.

[5] E.g. L.S. Cahill. Genetics, commodification and social justice in the globalization era. Kennedy Institute of Ethics Journal 2001; 11; 221-238.

[6] E.g. J. Christman. 1994. The Myth of Property: Toward an Egalitarian Theory of Ownership. Oxford. Oxford University Press.

[7] As a module in the MSc in Global Ethics at the University of Birmingham, for example.

[8] D.L. Dickenson. 1997. Property, Women and Politics. Cambridge. Polity Press. See also note 1.

[9] M.J. Radin. 1996. Contested Commodities: The Trouble with Trade in Sex, Children, Body Parts, and Other Things. Cambridge, MA, Harvard University Press, p. 2.

[10] D.S. Davis and S. Holland. Introduction. Kennedy Institute of Ethics Journal 2001; 11; 219-220, at p. 219. Original emphasis.

[11] R. Cox. 1997. Democracy in hard times: economic globalization and the limits to liberal democracy. In The Transformation of Democracy: Globalization and Territorial Democracy. A. McGrew, ed. Cambridge. Polity Press: 49-72, at p. 49.

[12] Ibid., p. 50.

[13] A.M. Honore. 1961. Ownership. In A.G. Guest, ed. Oxford Essays in Jurisprudence. Oxford. Oxford University Press.

[14] Ibid.

[15] A. Grubb. 'I, Me, Mine': Body Parts and Property. Medical Law International 1999; 3; 299-313.

[16] Christman, op. cit., note 6, p. 18.

[17] As, for example, in the *Moore* judgement, where the holding found no limitations on the rights of the researcher and the sponsoring university once it had been established that the plaintiff, Moore, had

none. (Moore v. Regents of the University of California. 51 Cal 3d 120, 793P 2d, 271 Cal Reporter 146.
[18] E.g. J. Penner. 1997. The Idea of Property in Law. Oxford. Clarendon Press.
[19] I have argued elsewhere (Dickenson, *Property, Women and Politics,* Polity Press, 1997) that it is by no means clear that we own our bodies, and hence our tissue. However, I have also argued there and in the articles cited in note 2 that women's labour in producing ova under the artificial and indeed dangerous conditions of 'egg harvesting' does in fact entail a Lockean right of property in one's labour and hence in the products of one's labour, such as ova.
[20] G. Calabresi and A.D. Melamed. Property rules, liability rules and inalienability: one view of the cathedral. Harvard Law Review 1972; 85; 1089-1128.
[21] For example, in the context of genetics, the UNESCO Declaration on the Human Genome, adopted in 1998 by the UN General Assembly, takes the strong but largely symbolic line that 'the human genome in its natural state shall not give rise to financial gain', in order to protect the 'heritage of humanity.'
[22] C.H. Harrison. Neither Moore nor the Market: Alternative Models for Compensating Contributors of Human Tissue. American Journal of Law and Medicine 2002; 28; 77-104.
[23] E.g. S. Wilkinson. 2003. Bodies for Sale: Ethics and Exploitation in the Human Body Trade. London. Routledge.
[24] S.C. Lawrence. 1998. Beyond the Grave—the Use and Meaning of Human Body Parts, a Historical Introduction. In Stored Tissue Samples: Human Legal and Public Policy Implications. R.F. Weir, ed. Iowa City, Iowa: Iowa University Press, 111-41. See also the story of the theft of the body of the last pure-blooded Australian aboriginal in Matthew Kneale's novel *English Passengers* (London: Penguin, 2000).
[25] I base my narrative on an account by the Director of the Tonga Human Rights and Democracy Movement, Lopeti Senituli: L. Senituli. They Came for Sandalwood. Now the B…s Are After Our Genes! Paper presented at the conference 'Research ethics, tikanga Maori/indigenous and protocols for working with communities.' Wellington, New Zealand: 10th-12th June 2004..
[26] Ibid., p. 3.
[27] Ibid., p. 3.
[28] Ibid., p. 4.
[29] Ibid., p. 4.
[30] H.M. Mead. 2004. Whakapapa and the Human Gene. Toi Te Taiao/The Bioethics Council. Wellington, New Zealand. The Bioethics Council.
[31] H.M. Mead. 2003. Tikanga Maori: Living by Maori Values. Wellington, New Zealand. Huia Publishers, at p. 45.
[32] E. Best. 1941. The Maori. Wellington. The Polynesian Society. Volume 1, at p. 39. Cited in Mead, op. cit., note 25, p. 47.
[33] Mead, op. cit., note 25, at p. 339.
[34] J. Patterson. 1992. Maori Values. Palmerston North, New Zealand. Dunmore Press, at p. 131.
[35] Toi Te Taiao/The Bioethics Council. 2004. Reflections on the Use of Human Genes in Other Organisms: Ethical, Spiritual and Cultural Dimensions. Wellington, New Zealand. The Bioethics Council. For example, one of the anonymous comments made to the Council in the run-up to the consultation was: 'They say they want Maori perspectives, but really they just want us to say yes or no to the questions they've already worked out. They don't realise that really getting Maori views would mean asking different questions.' It is to the credit of the Bioethics Council, however, that this comment is reproduced in the leaflet setting out the consultation exercise and inviting further similar or dissimilar opinions.
[36] Mead, op. cit., note 25, at p. 341.
[37] M. Durie. 2004. Mana Tangata: Culture, Custom and Transgenic Research. In Toi Te Taiao/The Bioethics Council. 2004. Reflections on the Use of Human Genes in Other Organisms: Ethical, Spiritual and Cultural Dimensions. Wellington, New Zealand. The Bioethics Council, 20-25.
[38] C. Waldby. Biomedicine, Tissue Transfer and Intercorporeality. Feminist Theory 2002; 3; 239-254.
[39] J. Moxon. 2004. Human Genes in Other Organisms: Ethical, Spiritual and Cultural Dimensions. In Toi Te Taiao/The Bioethics Council. 2004. Reflections on the Use of Human Genes in Other

Organisms: Ethical, Spiritual and Cultural Dimensions. Wellington, New Zealand. The Bioethics Council, 6-8.
[40] E.g. Waldby, op. cit., note 38.
[41] H. Widdows, D. Dickenson and S. Hellsten. Global Bioethics. New Review of Bioethics 2003; 1; 101-116.

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Emerging Regulatory Issues for Human Stem Cell Medicine[1]

KATHLEEN LIDDELL & SUSAN WALLACE

Abstract

The regulation of stem cell research is an issue that has drawn much comment, criticism and even judicial arbitration in recent years. An emerging issue, addressed in this article, is how the fruits of that research—stem cell medicine—are likely to be regulated en route from lab to market. Taking account of the ethical, legal, social and safety issues raised by stem cell medicine and the goals of governance, the article explains the relevant regulatory instruments (e.g. the draft UK Stem Cell Bank Code, the EU Directive on Human Tissue, the EU Directives on medical products and devices, and the Human Tissue Act 2004) and critically examines the framework they provide.

Introduction

Human stem cell research is an energetic and vibrant field of science across the world – not least in the UK, US, Israel, China, Japan and Australia. Nevertheless, it is also something of a political, ethical, social and legal minefield, creating challenges for regulatory bodies, policy makers and scientists as they traverse their way through a tangled web of regulations and moral prosthelytizing. Profoundly difficult questions surround the morality of destroying embryos or using the remnants of aborted foetuses to improve the medical welfare of other human beings, and the morality of cloning human beings to improve the efficacy of the technique.[2] There has been extensive public debate about these topics,[3] which led to two pieces of legislation in the UK,[4] numerous legislative amendments in other countries,[5] and calls for an international resolution by the UN General Assembly.[6]

But whilst there has been much commentary on the regulatory framework that is needed to govern the derivation of stem cells, there has been negligible discussion of the regulation that will govern how the results of this research—stem cell medicine—will get from lab to market. This article investigates this question. It seeks to explain how stem cell medicine is likely to be regulated, and to identify areas where further attention is required. These issues are significant as the UK has recently established a special Stem Cell Bank which will be the first in the world to curate standardized human adult, foetal and embryo stem cell lines on a single site.

We have structured our discussion in the following way. First, we draw attention to the issues that ought to be addressed by the regulatory system given the foreseeable characteristics of stem cell medicine. Second, we consider the regulation that currently applies during product development and when seeking market approval.[7] In this section we focus on the regulatory system that is developing in the UK. On the question of stem cell research, the UK is widely regarded as having produced some of the most sophisticated regulatory solutions. Its cautiously liberal approach has also positioned it as a world-leader in the development of stem cell medicine.[8]

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Furthermore a series of new initiatives (e.g. the UK Stem Cell Bank, the East of England Stem Cell Network and the Cambridge Stem Cell Institute)[9] and new legal policy from the UK and European Parliaments mean a concerted effort to regulate regenerative medicine is already underway. Some £16.5 million of public funding[10] and £200 million of further funding from the private sector have been earmarked for research related to the development of stem cell medicine.[11] These features make it a particularly interesting and relevant case study for the future regulation of stem cell medicine. In the final section we reflect on some of the tensions and gaps that remain in the fledgling UK regulatory system.

Regulatory Objectives

1 Potential medical applications of stem cell research

Stem cell medicine can be described as strategies for successful regenerative medicine to treat diseases and abnormal conditions of the human body. The idea common to all stem cell medicines is that they exploit the pluripotency of stem cells, which are cells that replicate in an undifferentiated state for long periods of time whilst retaining the potential to develop into most tissues of the human body. If current research is successful, scientists will be able to trigger stem cells to develop into different kinds of tissue. Newly generated tissue could then be transplanted to reconstruct diseased or dead tissue or to correct tissue function. Clinical applications might also be developed to stimulate patients' own stem cells *in situ*, for example to prevent osteoporotic fractures.[12]

Research is presently being conducted on a wide range of clinical applications. Examples include research to develop blood and bone marrow cells for treatment of blood diseases; pancreatic islet cells for diabetes; neural cells for nervous system repair; tissues to repair blood vessels; and engineered tissues to enhance ordinary tissue function.[13] Most of this research is still at an early stage, though stem cell medicine derived from fetuses has been the subject of clinical trials in the US[14] and cell lines are in preclinical development for studies with Huntington's Disease and sufferers of stroke.[15] Researchers are keen to develop methods of deriving stem cell lines from human embryos cloned from an adult donor, using cell nuclear transfer. These stem cell lines are more likely to be immunologically compatible with the donor. Thus far, clinical-grade human embryonic stem cell lines have not been developed.[16] Since most countries restrict or prohibit the use of embryos in research, further experiments are being done to investigate the pluripotency of stem cells obtained from adults and fetuses.[17]

There are a number of scientific challenges.[18] Most significantly, stem cells must be retrieved without damaging them, coaxed to create a stable cell line, and stimulated to differentiate into the tissue of choice. Having created the tissue of choice, it must be separated from the culture and reagents, transplanted to the area of the body without destroying or destabilising it, and made to integrate with other cells and the vascular system in the area of the transplant. It is important that the transplanted tissue does not infect the patient with a disease from the original stem cell or tissues used to culture it. Establishing inter-cell communication is also significant so that the transplanted stem cell tissue does not prompt an untreatable immune reaction or grow in an unresponsive way to create a tumour.

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2 Emerging issues for the regulatory system

The purpose of regulation, broadly conceived, is to facilitate a social goal—in this case the commercialisation of stem cell medicine—whilst addressing social risk, market failure and concerns of equity and morality through rule-based direction of social and individual action.[19] On one view it involves three generic sub-objectives. First, regulation must reassure the end-users (patients and health care providers) that the product will reliably satisfy their needs without creating undue cost or moral concerns. In addition to stimulating rational demand, regulation also needs to stimulate supply. That is, it must reassure those who supply raw materials and labour that it is an enterprise in which it would be rational to participate. In the case of stem cell medicine, biotech companies provide the labour and some raw materials. However, critical raw material—stem cells and oocytes—must be provided by ordinary people (some from IVF programs, some self-donors, some with unusual cells,[20] and some people off the street). A different set of conditions will be needed to attract their participation. A third objective of regulating commercialisation (often overlooked by economic analysis) is the importance of encouraging responsible manufacturing processes. This is the glue that holds the regulatory system together, securing compliance with the spirit of legal policy rather than companies doing 'what they can get away with'.

(a) Reassuring End-users

(i) Safety and quality

End-users are primarily concerned that the innovative stem cell medicines have a high level of safety and quality, and will not be detrimental to their health. In this regard, regulation will need to ensure that cell lines used as the basis for stem cell medicines do not carry an infectious disease, viral disease or mycoplasma contamination.[21] These might be transferred to the recipient of the stem cell transplant. At a research level, mouse feeder cells are often used to help culture human stem cell lines. These may have negative or unknown side effects in humans. Moreover, transplanting animal cells into humans raises the legal and ethical issues surrounding xenotransplantation. It is difficult to separate the mouse feeder cells once they have been used as a culture, thus regulation is needed to ensure appropriate culture bases are used for clinical-grade stem cell lines, and that research-grade and clinical-grade cell lines are kept separate. Similar steps are necessary to ensure that the reagents used during the cultivation of stem cell medicines are safe for human use. Two further issues relevant to the safety of the stem cell medicines are tumourgenicity and antibiotic use. These must be quantified and within acceptable levels. Antibiotics are commonly used to identify cells of interest in a culture or to clean up contamination, however this can interfere with inter-cell membrane communication or lead to antibiotic resistance.[22]

Stem cell medicine may also challenge typical assumptions about the relative risks posed by autologous[23] and allogeneic cell transplants.[24] The former are routinely regarded as less risky because there is less chance of infection and immune reaction, and the process is usually carried out within one institution. A question raised by stem cell medicine is whether cell lines from cloned embryos are to be regarded as autologous (i.e. a transplant from/to the same person), and whether they are indeed less risky.

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To ensure stem cell medicines are of a satisfactory quality, regulation should insist that cell lines have stable characterizations in order that the safety risks are predictable. Relevant indicators include karyotyping and chromosomal analysis, gene expression, proliferative properties, bioassays and telomerase activities.[25] Current indications are that freezing and thawing cell lines can affect stem cells' characterisation, therefore conditions of storage should also be addressed.

(ii) Clinical efficacy or performance of claims

Promoting high levels of quality and safety in stem cell medicine is a highly technical issue, but there is much agreement that this is an important goal. A more controversial issue is whether stem cell therapies should be required to show that they have equivalent or better therapeutic potential than other therapies already on the market. Alternatively, we might be satisfied if regulation simply stipulates that stem cell medicines must do what the manufacturer claims they will do (e.g. replace diseased tissue with tissue of a certain characterization). These contrasting standards are sometimes referred to as, respectively, 'efficacy' and 'performance'. The distinction goes to the heart of the difference between the regulation of medical products and medical devices. Medical devices (e.g. pacemakers and syringes) are required to show that they perform in the way the manufacturer claims and in this sense are regulated in a similar fashion to non-medical engineered products.[26] The question of efficacy is left largely to market forces; if the device is less useful than other therapies, consumers will not purchase it. In contrast, medical products (stereotypically, pharmaceutical drugs) are required to fulfil the more demanding criteria of efficacy,[27] and to this end manufacturers will more often be required to conduct clinical trials. Whether the regulatory system opts for performance or efficacy will be a particularly pertinent issue for a stem cell medicine if it carries a risk of causing abnormalities (e.g. tumours) which other alternative therapies based on drugs or live-transplant do not.

(iii) Cost-efficiency

The regulatory framework for stem cell medicines will also need to attend to the issue of cost-efficiency if it is to satisfy end-users. The health system has a variety of mechanisms to investigate the cost-efficiency of medicines (e.g. the National Institute of Clinical Excellence), but the most fundamental approach is to stimulate a competitive market. The general theory is well known. Where there is competition between sellers, consumers get a better deal. The sellers vie with one another to produce a better product at a cheaper price. The important drivers are that there should be enough sellers to provide a range of products at alternative prices, and informed consumers who rationally choose between the products on offer.

Innovative technologies like stem cell medicine pose difficulties for a properly functioning market. There may be few companies with the necessary know-how, new players may be inhibited by the regulatory burden, and consumers may lack the ability to distinguish the better product from a worse one. Consumers are especially likely to be information-poor if manufacturers are not required to prove the efficacy of their product prior to market approval. Thus there is a complex tension between keeping regulatory burdens low, and having enough regulatory intervention to protect unsuspecting consumers.

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(iv) Embryo origins

It is also foreseeable that end-users will be concerned about the origins of a stem cell medicine, in particular whether it is based on an embryo stem cell line. Should regulation stipulate that users should be carefully briefed about the fact that the medicine was produced from embryos? The extensive debate in this country and many others about the use of embryos in research suggests that a considerable number of people are unhappy with the prospect of using embryos for medical ends and would want to be carefully briefed about the provenance of the therapy and have the opportunity to refuse to use therapies built from dead embryos. An analogy would be the respect that is given to the decisions of Jehovah's witnesses to refuse the transfusion of blood or primary blood products.[28] On the other hand, perhaps this approach would be unduly cautious. After all we are rarely, if ever, informed whether medicines have been tested on primates and given an opportunity to refuse or consent on the basis of that knowledge though some people find experiments that use higher-order primates morally troubling. Does this fail to respect us as morally autonomous beings? Perhaps we are satisfied to receive medicines based on the understanding that the regulatory system has considered the issues, and has set and monitored standards that are reasonable for a morally pluralist society.[29]

(v) Social impact

A further issue which end-users might be concerned to see addressed by regulation is the justice of stem cell medicine and its impact on social relations. It has been suggested that minority ethnic groups are unlikely to benefit equally from stem cell medicine if stem cell banks fail to include the less common tissue haplotypes.[30] Furthermore, stem cell medicine may be a cost-intensive technology that only the wealthy will be able to afford. In the longer term it is possible that stem cell medicine may significantly extend average life expectancies, which has attendant social complications. For instance, pension payments and inter-generational family disputes could increase dramatically.

(b) Reassuring Suppliers

(i) Property, intellectual property and minimal regulation

By and large, companies that provide labour and materials will be reassured by the regulatory system if it includes mechanisms that provide for clear and secure chains of title, allows them to recoup investment through intellectual property, and keeps regulatory burdens minimal.

(ii) 'Respect' for tissue, consent and minimum standards

Securing the trust of members of the public who are the source of the precursor tissue for the stem cell lines may be more challenging. Donors of tissues may consider their tissue to have a value different from the value that researchers and manufacturers attach to it. Donors may project some of the significance they place on their identity, reproductive capacities, physical integrity, and immortality onto the tissue that they are asked to donate for the purposes of stem cell medicine. That is, they may see the tissue as more than the sum of its biological parts.[31] Their attitudes are likely to be highly variable and policymakers will need to consider how they should regulate in the face of reasonable pluralism.

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(iii) Incentives for stem cell donations

There is more debate whether regulations should provide incentives to make people more willing to donate their tissues, for example by paying them, or giving them some other benefit in return. Some are concerned that this would lead to an unethical level of commodification that belittles human existence, or undermines altruism.[32] Others have argued that safety is compromised when financial incentives are offered since donors will have a reason to hide information about their medical histories.

(iv) Confidentiality and feedback

Medical testing is part of the process of donating tissue for stem cell medicine, in order that the safety and quality of the tissue can be assessed. This involves screening for certain infectious diseases and genetic traits, and blood typing. This produces sensitive information that many donors may or may not wish to know, nor wish others to know. Therefore, the regulatory framework will need to protect the confidentiality of donors and set standards relating to feedback of information.[33]

(c) Encouraging Responsible Manufacturing Practice

Mechanisms to ensure responsible manufacturing practice are difficult to define precisely or exhaustively. In large part, the objective is to keep manufacturers sufficiently 'on their toes' so that they observe the regulatory policy, and sufficiently 'sweet' so that they cooperate with regulators without the need for costly prosecutions. In practical terms, this means stimulating a healthy level of competition, keeping regulatory burdens to a minimum, providing incentives in the form of intellectual property or free regulatory advice, and enforcing the regulatory framework sensibly (i.e. without extreme formalism or undue regulatory 'slack').[34] A pyramid system building up from self-regulation, registration and licensing, civil liability and finishing with a few criminal penalties for the worst breaches is argued by some to work well.[35]

Regulation: From Lab to Market

We turn now to consider the regulatory system emerging in the UK, as influenced by European and national legislation and policy.

1 Product Development

(a) EU Tissue Directive 2004

European Member States recently (March 2004) agreed, after protracted debate within the European legislative machinery, a common regulatory framework to ensure the safety of cells and tissues that are transplanted into, or onto, the human body.[36] One reason for the delay was that the European Parliament tried, indirectly, to prohibit therapeutic cloning and embryo stem cell research under this instrument.[37] Those provisions were eventually discarded.[38] The directive—titled "on setting standards of quality and safety of the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells"—will apply, amongst other things, to stem cell medicines but not the preceding *in vitro* research. Member States, and therefore the UK, are obliged to implement the directive by April 2006.

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The Articles most relevant to ensuring clinical-grade tissue development are those on testing, processing, donation, and procurement. The precise technical requirements are merely outlined in Article 28, and are yet to be decided by the Commission, pursuant to the procedures in Article 29. Draft technical requirements for donation, procurement and testing have been published for consultation.[39] A second set of technical requirements on processing, preservation, storage and distribution is expected in the near future. It is anticipated these will cover requirements for quality systems and coding.[40]

In broad terms, donated and processed tissue must be tested for infection (e.g. HIV, hepatitis and syphilis) and characterized. Living donors of allogeneic tissue are required to undergo a prior medical examination and interview. The Directive also stipulates that donors should not be paid, for reasons of safety rather than ethics.[41] Matters of ethics were regarded as issues that the European Union was not competent to legislate upon.[42] Issues of data protection and consent were covered to a limited extent. The Directive states that the European Directive on the processing of personal data must be observed[43] (this is already binding on Member States). It also states that the laws on consent in each Member State must be observed when tissue is procured from donors.[44]

Safety and quality are addressed in a set of rules on product recall, preservation, storage, labeling, packaging and adverse incident reporting.[45] No specific provision is made for compensation where a patient is harmed by a tissue therapy, although a claim might be made through product liability laws, including the law of negligence and consumer protection legislation.[46] It is doubtful however that these laws will assist an end-user who suffers emotional distress on finding out that they were treated with a product derived from embryos, but does not develop a recognized psychiatric condition.[47]

To ensure that the rules are adhered to and that the premises are suitable for the development of clinical-grade tissue therapies, each Member State is responsible for seeing that establishments that handle relevant tissue are licensed and follow a quality assurance system. Strict rules on the traceability of product development will also apply to achieve rigorous accountability.

The Directive does not apply to autologous grafts *within the same surgical procedure*.[48] The latter phrase is significant. For instance, if autologous tissue is banked it *is* covered by the Directive.[49] This suggests embryo stem cell medicine is likely to be covered by the Directive, whether or not it is considered an autologous procedure, since the activity required to clone a blastocyst is likely to require more than a single surgical procedure.

(b) Human Tissue Act 2004

Until the directive is implemented the standards noted above have no legal equivalent in the UK, aside from laws that protect donors of tissue. These laws, most notably the Data Protection Act 1998 and (until recently) the Human Tissue Act 1961, have been the source of much debate. Parliament has recently repealed the latter after the furore following the non-consensual retention of organs following post-mortems at hospitals in Bristol, Liverpool and elsewhere.[50] It has enacted in its place a much more extensive piece of legislation, the Human Tissue Act 2004 (HTA), which is expected to commence in April 2006. The fundamental principle underpinning this Act is that

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individuals should have the opportunity to choose whether or not tissue lawfully taken from their bodies is subsequently retained or used for medical research. Accordingly the Act makes it a criminal offence to use human tissue (excluding gametes and embryos) in research without the prior consent of the individuals. The Act also regulates tissue disposal, trafficking of controlled materials, and DNA analysis of tissue. However, somewhat surprisingly, the government's Explanatory Memorandum indicates that none of the various protections the Act introduces[51] apply to human stem cell lines by virtue of the clause which excludes tissue 'created outside the human body'.[52] This policy decision is perplexing in its ethical dimensions—surely donors of tissue for stem cell medicine are entitled to the same protection as donors of tissue for orthodox tissue transplants? The policy enacted goes well beyond the policies contemplated in the government's discussion paper preceding the legislation. These included the idea that *anonymised* cell lines might be used or stored without consent, or that donors might be asked to give up property and other economic rights in cell lines (but not all power to restrict the use of cell lines derived from them).[53]

(c) Codes and Guidance

(i) Tissue-related

To date, the safety of human tissue product development has been regulated by codes rather than law. The three principal codes in this regard were prepared by the Medical Devices Agency (MDA),[54] and the Department of Health.[55] The MDA's code includes rules on characterizing quality, batch control, infection controls, risk minimization, certificates of raw material analysis, scaffolds, donor screening, cell culture preparation, and full passage data. Other rules recommend procedures to prevent contamination, tampering and deterioration, and labels that advise on handling and hazards. The Department of Health's guidance is equally technical and detailed. The Codes were published in 2000 to 2002 and will need to be brought up-to-date for the purposes of stem cell medicine, particularly if stem cells are combined with nanotechnology and genetic technology to develop 'intelligent' regenerative structures.[56] In conjunction with these codes, the Medicines and Healthcare products Agency (MHRA) has encouraged therapeutic tissue banks to apply for voluntary accreditation.[57]

(ii) UK Stem Cell Bank

As noted, the UK has taken the bold new step of setting up a dedicated national Stem Cell Bank. It is the first in the world to curate standardised human adult, foetal and embryonic stem cell lines on a single site.[58] The Bank will house clinical-grade stem cell lines and establish approved facilities for processing them. It issued a Draft Code which broadly outlines the criteria to be observed when deriving and using human stem cell lines.[59] A companion code specifies the conditions for accessing stem cell lines in the bank.[60]

The Draft Code is ostensibly similar to the standards set out in the European Tissue Directive and codes on tissue therapies mentioned above. It also covers cryopreservation, import/export, and transportation of stem cell lines.[61] The International Stem Cell Forum has set up a working group to design indicators specially suited to characterizing embryo stem cell lines.[62] Sections 5 and 6 of the Draft Code set rules covering donor selection, screening, information and consent,

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and prohibiting payment. The central idea is that donors are asked to gift their stem cells, relinquishing all future control, after comprehensive information is provided to them about the implications of doing so. A further pre-requisite is that they consent to provide a medical history and allow genetic testing. Their data will be kept confidential, but traceable. Embryo donors may select one of three conditions for feedback on disease that might be discovered in the future (where it concerns their sample): no feedback; feedback where there is, or is potentially, a therapy; or feedback in any circumstance.[63] This contrasts with UK blood donation guidelines that, in an effort to minimise the numbers of donations that compromise public health, state that putative donors should be told that information about significant abnormal results *will* be fed back to them; blood donors are not permitted to stipulate that no feedback should occur.[64] To boost accountability to the standards, and avoid conflicts of interest, the Bank has decided it will not conduct discovery research itself.[65]

Not all stem cell developers will be bound by the Draft Code, only those who sign a contract to use stem cell lines from the bank. However, the principles are likely to reflect closely the MHRA requirements for market approval (see below), and the Medical Research Council (MRC) will require those who receive its funding to observe the Bank's rules.[66] The Draft Code will apply more strictly to embryo stem cell lines because the Human Fertilisation and Embryology Authority (HFEA) has decided that it will make compliance with the Draft Code a condition of all its licenses for embryo stem cell research, and will require a sample of all embryo stem cell lines to be deposited with the Bank.[67] One justification for the differential treatment of embryonic and somatic stem cell lines is that mandatory banking will minimize the numbers of embryos that are used, which some say is a mark of 'respect'.

The level of oversight seems to be tight. Detailed 'route maps' show the system for accessing a stem cell line.[68] The Bank has also indicated that, in relation to embryonic stem cell lines, its approval must be obtained before involving new collaborators from a different institution or new projects on the same cell line, and it should be notified of new and departing staff.[69] Nevertheless, the degree of real intervention remains unclear; the Bank may do little to enforce these requirements.

(d) Property and Intellectual Property Rights

The Draft Code from the UK Stem Cell Bank envisages that stem cell lines will remain the property of depositors, and that depositors will negotiate Materials Use Licenses with each would-be accessor to protect their proprietary interests.[70] Intellectual property rights can be asserted in these licenses. Some 'reach-through claims' could be expected (patent claims or license terms asserting a right to a share of revenue generated from downstream products, methods and protocols), but these are unlikely to be as controversial as reach-through claims stemming from gene patents, which cannot be invented around.

The UK Patent Office is willing to grant patents to applicants claiming pluripotent stem cell lines retrieved from human embryos,[71] as well as somatic stem cell lines (provided the standards of novelty, inventiveness, industrial applicability, sufficient disclosure are demonstrated). However, the European Patent Office's Opposition Division has interpreted the wording of the morality clauses in the EU Directive on the legal protection of biotechnological inventions differently.[72] On its view, the same policy would not be lawful under the European Patent Convention.[73] Unless the ruling is reversed on appeal, the implication is that inventors will have to

apply to national patent offices in each of the European countries where they hope to patent a stem cell line isolated from human embryos.[74] Until the interpretation of the EU Directive is clarified, individual Patent Offices are likely to adopt differing views about the patentability of stem cell lines isolated from embryos.

(e) Confidentiality and Feedback

Given that the EU Tissue Directive and the various codes stipulate that donors' samples and records should be traceable (meaning their identity is encrypted but accessible), it is likely that the data will fall within the definitions of personal data (under the Data Protection Act 1998) and confidential information (at common law). This would be the case where the data controller (a term defined under the Data Protection Act) holds the data encryption key, rather than an independent third party. In this case, users of the information would ordinarily need the consent of the person or persons who are identifiable from the information in the user's possession. The Data Protection Act 1998 is clear that this should be explicit consent, but neither it nor the common law clarify the specific information that must be given to ensure the consent is valid. The Annex to the EU Tissue Directive provides some guidance but this only applies in so far as it is consistent with Member States' national legislation and thus may not be binding.[75] Some scholars have also questioned whether genetic screening necessitates a special attitude towards consent, for example that consent should be sought from close family members prior to use or disclosure.

2 Market Approval

(a) Current Standards for Authorisation

Before a new medical product can be released, it must be approved for market release by the European Commission, or the UK Licensing Authority (Health Ministers) as advised by the MHRA. Strictly speaking, a new medical device does not require prior authorisation in the same way. A device is either 'self-certified' (the manufacturer declares the device meets the requirements under the relevant European medical device directive) or it passes a conformity assessment process with a 'Notified Body' (an independent (commercial) body which has been approved by the MHRA as suitable for carrying out such assessments). The crucial question is whether stem cell medicine is required to meet the criteria of the Medicinal Products Directive[76] or the less demanding Medical Devices Directive.[77] The answer is less than obvious if one looks to the central definitions of medicinal products or devices (see boxed figures 1 and 2).

Figure 1 Definition of Medicinal Product[78]

(a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
(b) any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis

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Figure 2 Definition of Medical Devices[79]

any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:
- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

Against these definitions stem cell medicines appear to be a borderline product. The distinction can be important as it affects the stringency of oversight. Furthermore, as mentioned, medicinal products are required to show clinical efficacy as well as safety and quality, and to this end a manufacturer must conduct clinical trials as necessary. With medical devices, on the other hand, manufacturers are (by and large) required to show only that a device performs as claimed and that its benefits outweigh the risks it poses to users. In practical terms, an evaluation of existing literature will frequently suffice and clinical trials are less commonly required.[80]

On closer inspection it appears that, at the present time, stem cell medicines will be treated as medicinal products since the Medical Devices Directive specifically excludes cells and tissues of human origin.[81] This categorisation is not an absolute rule,[82] nor a particularly apt one even after the Medicinal Products Directive was amended to include advanced technologies.[83] Thus the former UK Medicines Control Agency (MCA) and the former MDA (now amalgamated in the new MHRA) both took steps to set some indicative standards.[84] There are still some ambiguities and gaps. Tellingly, both the MDA and the UK Stem Cell Bank recommend that 'regulatory guidance should be obtained from the medicinal authorities on cell lines/tissues arising from stem cell technologies'.[85]

Interestingly the codes have narrowed the distance between the concepts of efficacy and performance. For instance the MDA code requests evidence that shows more than performance and states that 'where possible' developers should demonstrate 'a correlation with clinical effectiveness', and compare the product with the best clinical alternative for treatment through randomised clinical trials.[86]

(b) Proposed EU Regulation for Human Tissue Engineered Products

The vagueness within the current regulatory framework has led to considerable dissatisfaction:

> "At present, the lack of a comprehensive, clear and uniform regulatory framework creates legal uncertainties and leads to a fragmentation of the tissue engineering market: similar products are regulated differently in the various Member States, different safety requirements may apply and patients

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> can be denied access to products which are readily available in other countries."87

Some also consider the current rules deficient because the standards they set for autologous cell therapies are too lax in some circumstances. In response to these concerns, the European Commission has proposed a Regulation for human tissue engineered products, which it consulted on in 2002-2004.[88] It proposes a single regime for human tissue engineered products, clear demarcation from medicinal products and devices, and safety standards for autologous and allogeneic tissues that reflect levels of risk and minimize regulatory burdens for single application tissues. It is expected that a draft Regulation along these lines will be circulated for public consultation in 2005.[89]

(c) Clinical Trials Regulations 2004

As and when stem cell medicine trials begin, the new UK Clinical Trials Regulations (CTR), which came into force on 1 May 2004, will apply.[90] This instrument provides a statutory footing for good clinical practice, good manufacturing practice, research ethics committee review, informed consent of trial participants, and legal liability for injuries.[91] If a new Regulation distinguishes tissue-engineered products from medicinal products, the CTR may need amendment to cover these products.

The Adequacy of Current Regulation

1 Reassuring End-users

Many steps have been taken to ensure that the UK regulatory system promotes safe and high quality stem cell medicines, and addresses tumourgenicity, stability, adventitious agents, antibiotics use, freezing and the like. These apply to tissue generally and stem cell medicines specifically. Additional work is underway to improve the expertise and consistency of oversight.[92] It seems the authorities are also taking a holistic approach to the regulation of safety and quality, as evidenced by the introduction of regulatory mechanisms that apply long before a product seeks market approval and strict traceability.[93]

But whilst the issues of safety and quality have been thoroughly and openly addressed, other factors relevant to reassuring end-users have been neglected in comparison. One oversight has been the failure to discuss how the system will ensure compliance. To date, regulation has largely been soft rather than strict until the point at which MHRA approval is sought. This may continue even after the EU Tissue Directive and the Draft Code from the UK Stem Cell Bank are implemented.[94] The decision is relevant to the cost-efficiency of the system. The approach needs to improve the imperfections of the market, acting on behalf of information-poor consumers, without creating a weightier set of problems by adding regulatory red tape that hinders competition. The fact that there is only one UK Stem Cell Bank could create an anti-competitive bottleneck if it is not managed carefully. In effect, it has a monopoly on the banking of embryo stem cell lines and has a heavy responsibility to oversee those resources in an efficient manner.

There is also a question whether the system does enough to ensure manufacturers are sufficiently accountable to *patients* injured by stem cell medicines, as opposed to the official regulators. The myriad of codes does little to address this

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point. The Draft Code merely tries to exonerate the Stem Cell Bank of any responsibility, stating that stem cells are provided without any warrant of their merchantability or fitness for purpose.[95] Whilst consumer protection law might assist to some degree, a discussion about its adequacy is noticeably absent in the governance documents. These also fail to discuss the interest an end-user has in knowing that a stem cell medicine they are offered to them is derived from destructive research with embryos. The documents fail to discuss this even in the context of labeling.[96] Similarly, policymakers seem not to have considered the wider social issues relating to equity of access and resource allocation which academics have noted as being important. Further discussion is needed to establish how these matters might best be addressed.

There is also a lack of clarity on the issue of efficacy versus performance of manufacturers' claims. It is difficult to discern which standards manufacturers are required to meet, and it is odd that this issue was not discussed in the consultation documents on the proposed Human Tissue Engineered Products Regulation. There are empirical and normative issues at stake–for instance, how should one measure the efficacy of stem cell medicines; should efficacy be a *pre-requisite* for market-release of such an innovative therapy; and should the data on embryo-derived stem cell medicines be made available to the HFEA which must consider the necessity and desirability of license applications for the use embryos in research?

2 Reassuring Suppliers

In terms of its ability to reassure suppliers, the current UK regulatory system has some significant shortcomings, but is not acutely flawed. Policymakers have foreseen the issues of property and intellectual property in stem cell medicines. The Draft Code which has made provision for Materials Use Licenses, the UK Patent Office and the HTA have all taken steps to recognise explicitly developers' property and intellectual property in stem cell lines. Nevertheless, a good deal of uncertainty persists. Case law on the amount of skill and labour that is necessary to ground a property claim in human tissue is unclear (the HTA has not clarified it); and intellectual property rights available under the European Patent Convention (an administratively easier route than applying through national offices) are in a state of flux.

The developers of stem cell medicines must contend with a daunting regulatory burden, especially considering the majority of companies in this business are small- to medium-size enterprises. The applicable regulations are numerous, complex and growing, and their full impact will not be known until methods of compliance and enforcement become clearer. It may turn out that the variety of legislation is defensible as a tailored 'pyramid'. The UK Stem Cell Bank, together with its red tape, may also turn out to be a boon to smaller businesses if it lowers transactions costs and helps them develop compliance tools. We suggest this issue be monitored, and that State-sponsored initiatives to explain the regulatory system be introduced.[97]

Deeper problems surround the sufficiency of the regulatory system for protecting the interests of individual tissue donors. It is remarkable that donors of stem cells have the least legal protection of all tissue donors. Despite recent policy reform in the form of the HTA and the EU Tissue Directive, UK legislation does not stipulate that developers must respect the limits of stem cell donors' consent. For instance, if an individual were to state "I consent to you using my tissue to create a

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stem cell line, but in years to come I do not wish pharmaceutical companies to have access to the cell line because of the way my family was treated in a clinical trial", no liability would follow if the developer did in fact contravene the latter condition. Once a stem cell line is created, it falls outside the remit of the HTA. In contrast, conditions of consent will be binding under the HTA when other kinds of tissue are used by developers and even where pathologists inspect resected tissue for the purposes of basic research. If the developer thinks the putative donor's restrictions are unworkable, he or she is expected to avoid criminal liability by declining the tissue donation. Developers of stem cell medicines will perhaps decide to work in this way as well. But in the event they do not, donors whose tissue is used as a pre-cursor of a cell-line are left to rely on common law and the less formal powers of the UK Stem Cell Bank and the MRC. The latter two cannot force compliance from companies who develop somatic stem cell medicines with private funding and without using cell lines deposited in the Bank. Research ethics committees offer another line of protection, but at present it is doubtful whether they monitor compliance with consent requirements once they have approved a proposal. We leave open the question whether strict requirements for consent are the appropriate way to protect individuals' interests in their tissues, but would argue that the exclusion of stem cells from the HTA framework deserved considerably more debate. The question for present purposes is whether a legislative requirement should be added when the government implements the EU Tissue Directive, or whether individuals' interests in their tissues can be properly observed through another regulatory mechanism.

In terms of paying individual donors for their tissue donations, government resistance has shown signs of thawing[98] but payments will not be allowed at either the UK or EU level where cells or tissues are used for transplantation. It will take a groundswell to alter this position now that it has been backed by legislation. Therefore, it might be pertinent to consider other methods of motivating donors to donate.

The regulatory system does provide some reassurance in terms of donor confidentiality and rights to feedback. But its application is unfortunately vague and complex for the development of stem cell medicines, which involves incomplete anonymisation and compilations of genetic information.

3 Encouraging Responsible Manufacturing Practice

A number of positive steps have been taken to encourage responsible manufacturing practice in the UK. The UK Stem Cell Bank has signalled that it intends to work in partnership with industry to help them innovate efficiently, as well as to understand their ethical responsibilities. Furthermore, policymakers are aware of the importance of a level playing field[99] and have given industry opportunities to contribute to consultations. Together with the extensive range of standards, these steps go a long way towards maintaining an effective climate of respect and cooperation with the regulators. Maintaining this balance in practice will not be easy. Several critical issues are yet to be navigated. The authorities need to decide how they will check whether guidelines are being observed, and what they will do when they first notice that a licensee is not observing the legislation or guidelines. If the line they take is too tough, companies may cease cooperating and look more aggressively for ways to avoid the regulatory pinch or abandon the technology. If too soft, industry may come to regard ethical responsibilities as optional. Another issue yet to be tackled with

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vigour is biomedical companies' ethical duty to share the profits that derive in part from altruistic donations by members of the public.

4 A Final Word on Stem Cell Exceptionalism

Academic debate on the regulation of stem cell medicine is remarkable for its scarcity, but does this mean the issues are extraordinary and in urgent need of legislators' attention? We think this conclusion would be too strong. The scientific progress associated with stem cell medicine does not enter a regulatory vacuum. The law is designed to adapt to changing social circumstance. Nevertheless, there are several emerging regulatory issues that deserve closer scrutiny. None of these issues are unique to the regulation of stem cell medicine but quite a number are uncommonly encountered; for instance the s 54(7) exemption in the HTA, the new Stem Cell Bank with regulatory powers but no statutory standing, the interpretation of morality-based prohibitions on patenting in intellectual property law; unusual market dynamics and unfamiliar scientific risks (in particular in relation to autologous tissue transplants). In addition, we observed a number of issues that regularly arise in other fields of biolaw but which are no less important for being seen before. In summary, scant attention to methods of enforcement and compliance, vagueness about the criteria for market approval owing to the uncertainty surrounding the borderline between a product and a device, data protection law, information required for valid consent, the exceptions to the 'no property in the body or body parts' rule, and ethical debate about the extent to which the law should recognise donors' proprietary, economic and other rights in cell lines derived from their tissue. Hopefully these issues will be the focus of further inquiry by scholars from a wide variety of backgrounds without giving rise to a new kind of regulatory exceptionalism.

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[1] An earlier version of this paper was given at the Stem Cell Medicine and Public Policy course, 28-29 June 2004, Hinxton, UK, organized by the CGKP and Cambridge Centre for Stem Cell Biology and Medicine. A related paper by KL was presented at the Human Tissue Workshop, 20-21 January 2004, organized jointly by the CGKP and the King's College Bioethics Research Centre. Whilst remaining responsible for all errors and opinions, the authors would like to thank the participants at both these meetings for their insight on the science and policy issues, Alison Hall (CGKP) for her particularly thorough assistance on matters pertaining to the Human Tissue Bill, Dr Ron Zimmern (CGKP) and Sandra King (Mills & Reeve) for helpful suggestions on an earlier draft.

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[14] R.N. Rosenberg. Positive Potential of Fetal Nigral Implants for Parkinson Disease. Archives of Neurology 2004; 61:837-838.
[15] J. Sinden. Stem Cells and the Biotech Sector. Presentation at Stem Cell Medicine and Public Policy course, 28-29 June 2004, Hinxton, UK.
[16] On the most recent success: W.S. Hwang et al. Evidence of a Pluripotent Human Embryonic Stem Cell Line Derives from a Cloned Blastocyst. Science 2004; 303:1669-1674.
[17] C.M. Verfaillie. Adult Stem Cells: Assessing the Case for Pluripotency. Trends in Cell Biology 2002;12(11):502-508. The UK allows researchers to use embryos in research aimed at developing stem cell medicines but only where they obtain a licence from the Human Fertilisation and Embryology Authority (HFEA). The law states that the HFEA may only grant a licence where the proposed use of embryos in research is necessary or desirable. The HFEA announced in August 2004 that it had granted its first research licence to create embryos using cell nuclear transfer (cloning) to the International Centre for Life in Newcastle http://www.hfea.gov.uk/PressOffice/Archive/1092233888 (accessed 17/09/04). A special interest group has commenced proceedings for judicial review arguing that the licence was improperly granted, in part because the HFEA had not established that the research was 'necessary or desirable'. The High Court has agreed to grant a hearing on the matter. http://www.lawcf.org/dox/pdf_104.pdf (accessed 07/02/05).
[18] National Institutes of Health. 2001. Stem Cells: Scientific Progress and Future Research Directions. http://stemcells.nih.gov/info/scireport/ (accessed 27/07/04); European Science Foundation Policy Briefing. 2002. Human Stem Cell Research: Scientific Uncertainties and Ethical Dilemmas. http://www.esf.org/publication/142/ESPB18.pdf (accessed 27/07/04); European Commission. 2003, op cit note 12.
[19] Adapted from B Morgan and K Yeung. 2002. Regulation: Course Materials. University of Oxford.
[20] For example, there is some interest in establishing stem cell lines from schizophrenic patients (at present in order to identify new drugs): G. McAllister. Stem Cells and the Pharmaceutical Industry. Presentation at Stem Cell Medicine and Public Policy course, 28-29 June 2004, Hinxton, UK.
[21] President's Council on Bioethics. 2004. Monitoring Stem Cell Research. http://www.bioethics.gov (accessed 26/07/04).
[22] Draft Code [7.11].
[23] Autologous transplants are transplants where cells or tissue are obtained from one person and returned to the same person.
[24] Allogeneic transplants are transplants where cells or tissue are obtained from human sources other than the patient.
[25] J. Sinden. Stem Cells and the Biotech Sector. Presentation at Stem Cell Medicine and Public Policy course, 28-29 June 2004, Hinxton, UK.
[26] The essential requirements are found in Annex 1 of each of the three applicable medical device directives: 90/385/EEC (active implantable medical devices), 93/42/EEC (medical devices) and 98/79/EC (in vitro diagnostic medical devices). For example, Annex 1.3 of 93/42/EEC states that 'The

devices must achieve the performances intended by the manufacturer…'. On the performance standard, see: G Higson. 2002. Medical Device Safety: The Regulation of Medical Devices for Public Health and Safety. Institute of Physics Publishing, 163-4.

[27] Medicines Act 1968, s.19.1(b).

[28] See e.g. *HE v A Hospital NHS Trust* [2003] Family Law 733.

[29] One of us has elsewhere considered the theoretical foundation for the legitimacy and fairness of biolaw: K. Liddell. 2003. Biolaw and Deliberative Democracy. DPhil thesis; University of Oxford.

[30] H. Bok et al. Justice, Ethnicity, and Stem-Cell Banks. Lancet 2004; 364:118-121.

[31] C.A. McMahon et al. Embryo Donation for Medical Research: Attitudes and Concerns of Potential Donors. Human Reproduction (2003); 18(4):871-877, 874-875; M.J. Meyer et al. Respecting What We Destroy: Reflections on Human Embryo Research. Hastings Center Report 2001; 16, 18, 21.

[32] For critical discussion of the main arguments: S. Wilkinson. 2003. Bodies for Sale: Ethics and Exploitation in the Human Body Trade. London. Routledge; K. Baum. Golden Eggs: Towards the Rational Regulation of Oocyte Donation. Brigham Young University Law Review 2001; 107:134, 137, 158-9 (in relation to market incentives for oocyte donation); D.B. Resnik. The Commodification of Human Reproductive Materials. Journal of Medical Ethics 1998; 24:388, 393.

[33] See generally G. Laurie. 2002. Genetic Privacy. Cambridge. Cambridge University Press; J.V. McHale. Regulating Genetic Databases: Some Legal and Ethical Issues. Medical Law Review 2004; 12: 70-96.

[34] K. Yeung. 2004. Securing Compliance: A Principled Approach. Oxford. Hart. 158-162.

[35] I. Ayres and J Braithwaite. 1992. Responsive Regulation—Transcending the Deregulation Debate. New York. Oxford University Press.

[36] Directive 2004/23/EC.

[37] European Parliament (Committee on the Environment, Public Health and Consumer Policy). 25 March 2003. Report 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—A5-0103/2003. The Committee put forward an amended legislative proposal that prohibited the creation of human embryos solely for research purposes, research on embryos to supply stem cells, and research to supply stem cells through cell nuclear transfer (Art 4(2b)). Recital 13 added a further bolt to the door, stating that Member States 'must fully respect' the Council of Europe's Convention on Human Rights and Biomedicine, which in turn prohibits the creation of human embryos for research purposes (art 18(2)).

[38] European Parliament Daily Notebook for 16-12-2003: Human Tissues and Cells. http://www2.europarl.eu.int/omk/sipade2?PUBREF=-//EP//TEXT+PRESS+DN-20031216-1+0+DOC+XML+V0//EN&LEVEL=3&NAV=S#SECTION3 (accessed 07/02/05).

[39] European Commission. 3 August 2004. Draft Technical requirements for the donation, procurement and testing of human tissues and cells. http://europa.eu.int/comm/health/ph_threats/human_substance/oc_tech_cell/oc_tech_cell_en.htm (accessed 27/09/04). These reflect the indicative technical standards set out in appendices annexed to the draft directive (2002/C 227 E/28): See OJ 2002;C 227 E: 505-521.

[40] See http://www.hfea.gov.uk/HFEAPublications/EUTissuesAndCellsDirectiveNewsletter/EU%20%20Directive%20November%20merged.pdf (accessed 12/02/05).

[41] Recital 19.

[42] The Commission stated that it gave the ethical provisions suggested by the European Parliament 'careful consideration and can accept those related to the anonymity of donors and/or non-profit procurement …Other proposed ethical provisions cannot be accepted, however, as they fall outside the scope of Article 152, that provides for public health protection and not the implementation of ethical objectives as such.': European Commission. 28 May 2003. Amended proposal for the EU Tissue Directive (COM(2003) 340 final), para. C(1).

[43] Article 14; Recital 24 referring to Directive 95/46/EC.

[44] Article 13. In the UK, relevant laws include the Data Protection Act 1998, the common law of confidentiality, the HTA 2004 (for tissue obtained from deceased persons), the Human Fertilisation and Embryology Act 1990 (for donations of embryos and gametes), and the law on battery and negligence (for tissue obtained from living persons).

[45] Articles 11, 21 and 22.

[46] The EU directive simply stipulates that member states shall set 'dissuasive' penalties (Art 27), which suggests that criminal liability or revocation of licence will follow a breach.
[47] A successful action under the Consumer Protection Act 1987 is also made difficult by the controversial 'development risks defence', under which it is a defence for the producer to show that, at the relevant time, the state of scientific and technical knowledge was not such that he could be expected to discover the defect. In other words, the technology was so new and unfamiliar that the producer could not be expected to have recognized the defect.
[48] Article 2(1).
[49] Recital 8.
[50] For background on the retention of human tissue without relatives' consent: Learning from Bristol: The Report of the Public Inquiry into Childrens' Heart Surgery at the Bristol Royal Infirmary Cm. 5207 (2001); Report of the Inquiry into the Royal Liverpool Children's Hospital (Alder Hey) HC 12-II (2001); Department of Health The Investigation of Events that followed the death of Cyril Mark Isaacs (2003a); Department of Health Isaacs Report Response (2003); Department of Health Human Bodies, Human Choices—The Law on Human Organs and Tissue in England and Wales – a consultation report (2003).
[51] For example, the provisions dealing with appropriate consent, storage, use, discard, trafficking controlled substances, and DNA analysis of tissue.
[52] s. 54(7). Lord Warner confirmed the Government's intention during the Bill's second reading in the House of Lords: 'Cell lines are excluded from the Bill…because it applies only to human cells coming directly from a human body.': Lord Warner. 22 July 2004. Hansard. House of Lords. Column 430.
[53] Department of Health. 2003. Human Bodies, Human Choices—The Law on Human Organs and Tissue in England and Wales – a consultation report. [17.22]-[17.23]. Department of Health. 2003. *Human Bodies, Human Choices—Summary of responses to the consultation report*. [2.23].
[54] Medical Devices Agency. 2002. Code of Practice for the Production of Human-Derived Therapeutic Products. ('MDA Code').
[55] Department of Health. 2001. Code of Practice on Tissue Banks; Department of Health. 2000. Guidance on the Microbiological Safety of Human Organs, Tissues and Cells Used in Transplantation.
[56] G. McAllister. Stem Cells and the Pharmaceutical Industry. Presentation at Stem Cell Medicine and Public Policy course, 28-29 June 2004, Hinxton, UK.
[57]See http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Tissue/TissueGeneralInformation/TissueGeneralArticle/fs/en?CONTENT_ID=4077127&chk=8MjvZR (accessed 21/07/04).
[58] The UK Stem Cell Bank project began 1 January 2003; the Bank was officially launched and the first cell lines deposited on 19 May 2004. The Bank is sited at the National Institute for Biological Controls and Standards in Hertfordshire, UK. http://www.ukstemcellbank.org.uk/ (accessed 29/09/04).
[59] Steering Committee. 2004. Draft Code of Practice for the Use of Human Stem Cell Lines—version 1, March 2004. (Draft Code). http://www.mrc.ac.uk/index/public-interest/public-consultation/public-stem-cell-consultation/public-use_of_stem_cell_lines.htm (accessed 22/07/04). Consultation period closed 28 May 2004.
[60] Steering Committee. 2004. Interim Code of Practice for the UK Stem Cell Bank—version 1, April 2004. http://www.mrc.ac.uk/index/public-interest/public-consultation/public-stem-cell-consultation/public-bank_code_of_practice.htm (accessed 22/07/04). ('Interim UK HSC Bank Code') The interim code is to be revised once the Draft Code is finalised.
[61] Draft Code [7.12], [12], [7.7].
[62] See http://www.stemcellforum.org/registries_&_banks/characterising_cell_lines.cfm (accessed 26/07/04).
[63] Draft Code [6.6]. No explanation is given for limiting the feedback options to embryo donors, and not offering them to somatic cell donors.
[64] UK Blood Transfusion & Tissue Transplantation Guidelines. 2002. 6th edition. See [23.6]. http://www.transfusionguidelines.org.uk/uk_guidelines/ukbts6_228.html (accessed 27/09/04).
[65] Draft Code [2.3], [6.3], [15.2].
[66] MRC. Research Involving Human Stem Cells: supplementary terms and conditions to be applied to new an extended MRC grounds, MRC unit programs and MRC training awards from 1/08/2003 http://www.mrc.ac.uk/pdf-terms_conditions_stem_cells.pdf (accessed 26/07/04).
[67] Draft Code [2.4], [3], [9.1], [11.1]. Strictly speaking, it is questionable whether the HFEA has legal power to make the Stem Cell Bank code binding on those who apply for its licences, since its statutory

powers apply to the creation and storage of embryos and the storage of gametes. Stem cell lines are neither embryos nor gametes. Section 1(3) of the Human Fertilisation and Embryology Act states 'this Act, so far as it governs the keeping or use of an embryo, *applies only to keeping or using an embryo outside the human body*'. (emphasis added). The HFEA is relying on a broad interpretation of its power to license embryo research. It asserts it has the power to limit how the *results* of that research can be used. By way of analogy, this is akin to an authority with power to regulate the use of apple trees exercising power over apple juice. Schedule 2(3) of the Act limits the types of research that may be licensed, but says nothing about the restrictions the HFEA may specify. The Courts might allow the HFEA wide latitude if it can establish that the restrictions are reasonably connected with showing respect for the moral status of embryos.

[68] Draft Code [9].

[69] MRC, op cit note 66.

[70] Draft Code [15.3].

[71] UK Patent Office, 'Practice Note: Inventions Involving Human Embryonic Stem Cells' (UKPO, April 2003) http://www.patent.gov.uk/patent/notices/practice/stemcells.htm (accessed 07/02/05). Totipotent embryo stem cells are not patentable because these have the capacity to develop into a human being, and hence fall foul of the prohibition against patenting the human body at a stage of its formation (Patents Act 1977, sch A2 3(a)). Processes for obtaining stem cells from human embryos are also not patentable because such inventions involve the use of a human embryo and are thus contrary to the Patent Act 1977 sch A2, 3(d).

[72] Directive 98/44/EC Art 5, 6.

[73] Edinburgh Patent (EP 94913174) EPOD 21/07/03, considering EPC Art 53(a) and rules 23d(c), 23e(1).

[74] Commercial secrets might be protected despite mandatory banking because third parties will not be granted access until depositors and accessors have agreed a Materials Use Licence: Draft Code [15.3].

[75] Art 13; Annex. The Annex suggests that if donors are to be properly informed they should be told the therapeutic purpose of procurement, consequences and risks of donation, analytical tests conducted, data recorded, levels of confidentiality, their right to access confirmed and explained results of the analytic tests, and other safeguards.

[76] Directives 65/65/EEC and 2001/83/EC (restatement).

[77] Directive 93/42/EEC.

[78] Directive 2004/27/EC recently amended the definition of medicinal products in Directive 2001/83/EC. The latest definition, reproduced here, is incorporated in UK law through the Medical Devices Regulations 2002 and the Medicines for Human Use (Clinical Trials) Regulations 2004.

[79] Directive 93/42/EEC, Art 2(a). This definition is referred to in the Medical Devices Regulations 2002 (UK). Separate definitions cover *in vitro* medical devices (98/79/EC) and active implantable devices (90/385/EEC).

[80] C. Hodges. 'European Regulation of Medical Devices'. In J.P. Griffin and J. O'Grady, 2003. The Regulation of Medical Products. London. BMJ Books; 83, 100.

[81] Directive 93/42/EEC, Art 1(5)(f), and Medical Devices Regulations 2002 (UK) s 3(d). It has been suggested that this exception was included because it was envisaged that cells and tissues of human origin would be satisfactorily covered by legislation on tissue/cell banking and blood products: Lloyd-Evans, 2004, op cit note 7, 52. The former legislation has not yet come to pass, and the latter is too narrow for recent technology.

[82] The non-biological part of the stem cell-based device might be governed by the Medical Devices Directive: Lloyd-Evans, op cit note 7.

[83] Directive 2003/63/EC.

[84] MDA code. Memorandum by the Medicines Control Agency. In House of Lords Select Committee Report on Stem Cell Research 2002 (Evidence), 256-7. The MCA advised that 'certain' stem cell products fall 'under the broad heading of "[somatic] cell therapy product".' See also EMEA Committee for Proprietary Medicinal Products. May 2001. Points to Consider on the Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products CPMP/BWP/41450/98, 10.

[85] MDA code [2.1]. See also Draft Code, 13. The MHRA can provisionally determine whether a product is a 'medicinal product'. This decision may be reviewed by the Independent Review Panel. These unusual measures indicate the degree of ambiguity surrounding the definitions.

[86] MDA code p 5, 21-22. It also recommends that evidence be collated to show 'the expected benefits to the patient' and efficacy, rather than just an absence of toxicity. The Draft Code states that

developers should demonstrate that the therapy is 'effective in delivering the expected benefit to the patient': at 14.

[87] European Commission. Proposal for a Harmonised Regulatory Framework on Human Tissue Engineered Products: DG Enterprise Consultation Paper (Brussels, 6 April 2004) p 3 http://pharmacos.eudra.org/F3/human-tissue/index.htm (accessed 07/02/05).

[88] European Commission, ibid; and Summary of Contributions. EC Regulations, as written, are community law and must be applied directly in Member State law. Directives, on the other hand, allow Member States to decide how to incorporate the objective of the directive within their own domestic legal systems. Therefore, a Regulation for tissue engineered products should "…ensure uniform and timely application of the rules…": Summary of Contributions.

[89] See http://devices.mhra.gov.uk/mda/mdawebsitev2.nsf/7d802374dabdd36600256a760041066d/6cb284dbc2cc285280256be40036dd70/$FILE/TissueEngineeringLetter.pdf (accessed 14/02/05).

[90] The Medicines for Human Use (Clinical Trials) Regulations 2004.

[91] One of us has elsewhere written on the impact of the CTR, see: S. Wallace, 2004. The Impact of the Draft UK Medicines for Human Use (Clinical Trials) Regulations 2003 on Research Ethics Committees. Ph.D. Thesis. University of Sheffield, Department of Law.

[92] E.g. the proposal for a Human Tissue Engineered-Products Regulation.

[93] The Codes and especially the EU Tissue Directive, which has legal force.

[94] The UK Stem Cell Bank does not have formal powers for inspection and monitoring. The new Human Tissue Authority will be responsible for implementing the EU Tissue Directive (if it can overcome cl 59(7) of the HTA). The government has announced plans to merge the HTA with the HFEA to create the Regulatory Agency for Fertility and Tissue (RAFT). There is some speculation that the HFEA's strict licensing (which have not been popular with IVF clinics) will influence the Human Tissue Authority. Alternatively, the merger may be a catalyst for change within the HFEA.

[95] Draft Code [8.5].

[96] The Draft Code suggests this will be reviewed at a later date: [6.2.2.4].

[97] State-sponsored initiatives such as the Regulatory Advisory Service to Bio-tech Agencies, sponsored by the East of England Development Agency, might also help SMEs adjust to the regulatory burdens in this field.

[98] The Human Tissue Bill was amended during Parliamentary debates so that the prohibition against financial payments is limited to materials intended for transplant: see HTA s 32(8)(c).

[99] This is clear from the incorporation of Good Manufacturing Practice and Good Clinical Practice in the Clinical Trials Regulations, and from recent consultation on a Human Tissue Engineered Product Regulation.

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The New Human Tissue Bill: Categorization and Definitional Issues and their Implications.

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Abstract

While providing a welcome and timely revision of the now outdated Human Tissue Act of 1961, the newly introduced Human Tissue Bill of 2004 contains a number of anomalies in its drafting that threaten to undermine its effectiveness in practice. Two examples: the first relating to the status of 'remnant or waste' tissue and the second relating to the status and use of artefacts created from collected tissue are here employed to illustrate some of the definitional and categorical inconsistencies that are evident in the Bill. Having identified these, the paper then provides an analysis of how these inconsistencies may act to severely constrain the ways in which retained tissue may be lawfully employed in biomedical research and to confuse questions of who may, or may not, have formally recognised interests in types of processed human tissue.

Introduction

The new Human Tissue Bill of 2004 has been drafted largely in response to concerns raised by events at the Bristol Royal Infirmary and the Royal Liverpool Children's Hospital (Alder Hey). As the Kennedy [1] and Redfern [2] inquiries established, organs and tissue from children who had died at these two hospitals had been removed, stored and used without proper consent, a matter of grave concern. A subsequent census by the Chief Medical Officer for England (2000)[3] and the Isaacs Report (2003)[4] revealed that the practice of retaining, storing and using organs and tissue taken from adults and children without proper consent had become relatively commonplace in the period from 1970 to 1995. There was a considerable expectation that the new Human Tissue Bill would provide a welcome means of remedying the insufficiencies in existing legislation that had allowed these wholly unacceptable events to occur and that it would establish a clear and workable framework of governance for the collection and use of human tissues and organs in the UK.

Following the tabling of the first draft of the Bill in the House of Commons on the 3rd December 2003, it became evident, however, that the new Bill contained a number of vagaries and inconsistencies that threatened to undermine its effectiveness in practice and constrain vital medical research in ways perhaps not fully anticipated by those responsible for its introduction. In order to draw attention to the implications of the passage of the Bill, and its likely effect on biomedical research in the UK, an interdisciplinary Human Tissue Bill workshop (jointly sponsored by the Wellcome Trust-funded King's College Bioethics Project and the Cambridge Genetics Knowledge Park) was held at King's College, Cambridge in January 2004. The workshop, which drew together 40 invited delegates with expertise in medical research, law, pathology, and the social sciences, identified a number of areas of

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immediate concern. These, and a series of possible amendments to the Bill, were robustly debated, and the latter circulated within the broader bio-medical community for further consultation and refinement before being advanced for consideration. The Bill returned to the House of Commons for its report stage and third reading on the 29th June, 2004. Of the nearly 100 amendments that were eventually tabled, four significant ones were finally adopted. The Bill is currently being vigorously debated in the House of Lords.

As an online briefing paper produced by the co-ordinators of the workshop provides a detailed summation of the main shortcomings of the Bill[5] (as originally drafted), my aim here is to employ just two examples (the first relating to the status of 'remnant or waste', the second relating to the status and use of artifacts created from collected tissue) to illustrate some of the ways in which the Bill was initially insufficient, how subsequent amendments may address these insufficiencies, and what may yet be required to ensure that the Bill operates in an effective and equitable manner. What becomes evident from this analysis is that many of the most potentially problematic aspects of the Bill arose out of definitional and categorical inconsistencies – that is to say, inconsistencies in the way the Bill defines its subject matter and categorizes the uses to which that subject matter might be put, both medically and commercially. Unless remedied, they have the potential (now somewhat, but not fully ameliorated), to severely restrict how retained tissue may be used in biomedical research and to confuse questions of who may or may not have formally recognized interests in types of processed human tissue – for example, property rights in them or rights to deal in them commercially. The following sections outline the primary issues and areas of remaining concern.

Remnant and 'Waste' Tissue: To what should the Human Tissue Bill apply?

One of the most important outcomes of the Alder Hey and Bristol enquiries was the recognition that there was a very serious disjunction or lack of correspondence between pathologists' and the general public's perceptions of what might constitute 'a sample of tissue'. Many parents were gravely distressed to discover that retained 'samples of tissue' had in some cases, included whole organs or very sizeable parts of them. Some wished only these identifiable organs or parts to be returned to them for burial, others argued that as all body parts were as significant as each other, all retained samples of tissue should be returned to them, even those which had been subsequently turned into technological artefacts such as tissues slides and blocks. It became clear politically, that, in the circumstances, it could well be construed as an affront to bereaved parents to suggest that body parts be 'hierachised' in any way under the new law. It is as a direct consequence of this, I believe, that the new legislation adopts, in Section One of the Bill, a deliberately broad definition of the category of objects to which the Bill will generally apply. This includes all "relevant material of which the body consists, or which it contains'. Relevant Material is explicitly defined in Section 58 (1) as 'material, other than gametes, which consists of, or includes human cells'.

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Employing such a broad basic definition of the material to which the Bill would apply was useful to the drafters as it enabled them to send out an unequivocal signal to a mistrustful general public that the Bill would legislate against all unconsented uses of every conceivable variety of human bodily part no matter how obtained or constituted. The difficulty lay in the fact that the definition was also, necessarily, wholly un-nuanced – few distinctions were made between different types of body parts and bodily derivatives and little account was taken of the quite different circumstances in which they were acquired or produced. Each were to be treated commensurately under the new law despite the fact that, in general, the interests (both personal and legal) that individuals have in these materials is mediated by factors such as the nature of the material, (what type it is, its size, etc.); the manner in which was collected; and the prospective uses to which it might be put. The broadness of the basic definition of the 'relevant material' to which the Bill would apply was such that that a number of exceptions had to be made to it in order to render the Bill operable in practice. The rationales for excepting them were also, however, characterized by inconsistencies, as we shall see.

Sections 1.1 of the first draft of the Bill, set out the consents required to lawfully remove, store and use organs and tissues. Very significantly, no distinction was here made between the specificity and scope of the consent required for the storage and use of 'relevant material' from that of the dead or that of the living for purposes set out in Part One of Schedule I – which included education or training relating to human health and general medical research into disorders or functioning of the human body. Neither, by consequence of the application of the all-encompassing definition of 'relevant material' was any distinction made between the types of material to which the legislation would pertain. No distinction was made, for example, between a whole organ removed post-mortem and a sliver of tissue or even a few cells taken as a biopsy for diagnostic purposes during life. The draft Bill had it that it would be possible to employ tissue obtained from a living subject without their consent, but only for the very limited range of uses set out in Part 2 of Schedule I. These included clinical audit, education or training incidental to medical diagnosis or treatment, quality assurance and public health monitoring. The explanatory notes that accompany the Bill make clear that these activities are exempted from the usual consent requirements, as they are 'considered intrinsic to the proper conduct of a patient's treatment or are necessary for the public health of the nation'.[6]

This drafting gave rise to several serious concerns. The first was that the new legislation, if enacted as drafted, would make it a criminal offence to store, remove or use any 'relevant bodily material' from a living person for the purposes of education and training, or research into functioning or disorders of the human body, without their 'appropriate' consent. It became immediately evident that this would, as a consequence of the broadness of the definition of 'relevant bodily material,' necessarily include all blood samples and tissues taken for diagnostic purposes during a patient's lifetime along with any remnant or waste tissue retained following surgery, and cells aspirated from biopsied materials during surgery or diagnosis, even urine and sputum. Such materials have long provided an invaluable resource for use in bio-medical research, training and education, and there was a strong consensus within the

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medical and research communities that to make it a criminal offence to utilise them without the consent of the individual would act to profoundly constrain essential research activities.

As a direct consequence of the circumstances of its production, the first draft of the Bill was underwritten by a presumption that individuals have an undifferentiated relationship to their extracted body parts: that they consider all body parts to be as significant as each other, regardless of their form or the circumstances of their detachment. While parents, partners and significant others often express this sentiment in relation to the collection and use of body parts taken from those to whom they have a duty of care,[7] own research and that conducted by the Peterborough Tissue Resource Centre [8] suggests that individuals do not always display the same degree of sentiment about their own body tissues. Many seem to care remarkably little about the fate of organs or tissues lost to them in life, and are particularly unsentimental about tissues, cells or fluids extracted for surgical or diagnostic purposes. Some however, feel more strongly about whole organs removed during post-mortems as this is a practice that threatens the principle of maintaining bodily integrity in death to which many people subscribe.

In 1995 the Nuffield Council Report "Human Tissue: Ethical and Legal Issues" controversially argued that any material excised surgically, could be regarded as "abandoned" or "discarded" by the patient. As the material was res nullius - a thing which never had an owner, or which had, but lost its owner- it would therefore become available to be employed for a variety of legitimate purposes, including research. Following the Alder Hey and Bristol enquiries, the MRC set out more restrictive guidance on the use of such materials, recommending that, whenever practicable, individual patient consent be obtained for use in research of human material surplus to clinical requirements. This principle was enshrined as a legal requirement in the first draft of the Bill despite the fact that the Response to Human Bodies Human Choices Report recommended that 'any new legislation take account of the different emotions attached to human organs and tissue removed from the living and those who have died'[9].

There seemed consequently to be very sound reasons to consider re-drafting the Bill in order to create a distinction between a) the use of residual tissues taken with proper consent in a clinical situation and b) the explicit removal and storage of whole organs at post-mortem specifically for research or other purposes. While explicit consent would be required for the latter, it did not seem inappropriate to consider whether it might be made lawful to use the former for research and other ethically approved purposes without specific consent.

A second very serious concern was that relating to the specificity of the consents required to use residual tissue in a lawful manner. Although the Bill introduced criminal sanctions for those found to have retained or used such material without 'appropriate consent', at no point did it state on the face of the Bill what form such a consent would take – whether, for example, it would be satisfied by the procurement of a verbal or written consent, and whether or not a broad consent given at the time of

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treatment would be sufficient to cover prospective or unanticipated uses of the material. The logistical implications of having to secure a detailed consent from individuals to use their remnant tissue and other bodily samples for purposes within Schedule 1 (as initially drafted) were bought home by some initial estimations proffered by Professor Peter Furness[10] who calculated (based on figures extrapolated from workload data in the Leicester region of the NHS that some 150 million specimens were collected each year from living persons in Britain. Allowing even just one minute per patient to explain the consent procedure, offer information and record the patients response, Furness estimated that fulfilling the consent requirements as first drafted would demand at least an extra 1,339 full time jobs and substantial refinements of existing computerised recording facilities.[11]

A third concern was the apparently arbitrary and unsustainable distinctions that were being drawn in the categorization of research activities. While, for example, epidemiological research for the purposes of public health monitoring and clinical audit was placed in schedule 2, and thus able to be carried out on remnant tissue from living persons without their explicit consent, all other types of general epidemiological research requiring the use of remnant samples were placed outwith Schedule 2. As members of the Academy of Medical sciences noted in their January statement on the matter there is, in reality, often very little distinction between public health monitoring and clinical audit research, and general epidemiological research carried out to determine the distribution and determinants of disease risk in human populations.[12] Despite this they were to be categorised quite differently in law under the new Bill. So, while determining the proportion of women attending antenatal clinics who are hepatitis B positive or HIV positive would have been defined as an example of 'public health monitoring', a Schedule two activity not requiring consent, establishing the relationship between the proportion of people with and without heart disease who are Chlamydia positive to see if Chlamydia infection may be a cause of heart disease, would be categorised as a Schedule I activity requiring consent. As they noted, there seemed no logical reason why these two activities, which are fundamentally commensurate, should be treated as categorically distant or requisite of different treatment in law, at least as far as consent requirements are concerned. Why this research, or indeed all research carried out in connection with disorders, or the functioning of the human body could not reasonably be categorized as also being "intrinsic to the proper conduct of a patient's treatment or necessary for the public health of the nation" – the rationale for placement of an activity in Schedule 2, was also unclear.

Amendments and outstanding issues

Following the workshop, and a period of intensive lobbying by bio-medical research groups and institutions, a number of amendments were made to the Bill. The new sections 1(7); 1(8); 1(9) and Schedule 5 Paragraph 10 have the operative effect of placing research in connection with disorders or functioning of the human body into Schedule 2 of the Bill without doing so overtly. The need to effect this transference was evident, however the political sensitivities were such that this outcome had to be achieved through a somewhat circuitous route. Sections 1 (7-9) of the Bill allow tissue

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from the living to be stored and used for some education and training purposes and for research in connection with disorders or functioning of the human body (including genetic research – Schedule 5 Paragraph 10) without consent if two criteria are met: The first is that the research be "ethically approved in accordance with regulations made by the Secretary of State" and the second is that it be "carried out in circumstances such that the person carrying it out is not in possession, and not likely to come into possession, of information from which the person from whose body the material has come can be identified". Obscurantist language aside, this means anonymised, such that the identity of the donor can no longer be linked to, or derived from the sample.

This very substantive and warmly received set of amendments will undoubtedly ensure that most types of essential bio-medical research conducted in the UK can now proceed with appropriate safeguards but without being overly consumptive of precious financial or administrative resources. While there is much to be welcomed in the amendments some anomalies remain that will impede vital research initiatives unless they are remedied before the final passage of the Bill into law. The most pressing of these relate to the requirements for anonymisation. While in most cases it will not be necessary for researchers to link tissue samples to clinical information about the donor, in some areas of epidemiological research, particularly genetic research, it will remain essential to do so. At Georgetown University in the United States for example, there exists an archived bank of nearly 2000 samples of tissue drawn from women with breast cancer that is linked both to clinical data on their treatment: type and duration, response to treatment, relapse and survival rates, as well as sociodemographic and genetic data on potential risk factors, such as alcohol, reproductive history and occupation.[13] Although such information can be irreversibly anonymised in order to prevent identification of the donor (as would be required under the new HTB as currently drafted) it is not always desirable to do so.

As Bill Lowrance noted in his 2002 report for the Nuffield Trust on the secondary use of personal data in health research,[14] there are a number of crucially important reasons for retaining the potential to re-identify and/or re-trace donors. These include the need to allow validation or auditing of the data; to request additional data if necessary; to inform a physician or patient of useful findings; and to facilitate later research follow-up. Reversible anonymisation allows patient identifiers to be replaced with a code that can be accessed only by a select few 'key holders' who have the power to re-associate the de-identified data with the original identifiers should this become necessary to undertake any of the tasks outlined above. Unless the Bill is redrafted such that the definition of anonymisation is clarified to ensure that reversible anonymisation will be acceptable in certain specific circumstances, the quality of much epidemiological research will be seriously compromised.

As the wording of the Bill stands at present, it seems that it will also be impossible for any clinician who is in direct contact with a patient to undertake any form of research on that patient as he or she would inevitably be in possession of identifying information about them. While the intention is to ensure that the privacy of the research subject is not compromised the current wording will also ensure that no

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clinician will be legally entitled to undertake research on any of his or her patient groups even if the research is essential and has been approved by an ethics committee. Ron Zimmern, Director of the CGKP notes that the Medical Research Council have advocated that the Bill should permit the use of tissue for research without anonymisation, if the results cannot effect the person's or the families interests and where the patient has been informed at the time the sample was taken that their material may be used for research subject to approval from an appropriately constituted research ethics committee, and that this kind of exception ought to be formalized in the new legislation to prevent criminalisation of legitimate research activities undertaken by clinicians on known patient groups.[15]

While the amendments have seen the use of tissues from living donors for the purposes of education and training relating to human health moved from Schedule 1 to Schedule 2 of the Bill, the use of tissues from either living or dead persons for the purposes of education or training relating to research remains an activity for which consent much always be secured. The rationale for creating a categorical distinction between the two is weak at best, if not wholly unsustainable and there again seems no logical reason why it should not become lawful to use remnant tissue from living donors for any purposes relating to bio-medical education or training subject of course to the MRC's caveats that it not adversely affect their or their families interests; that they have been informed at the time that the sample was taken that it may be used for this purpose; that its use in training or education be subject to the usual ethical approvals; and that they may opt-out if they wish.

Finally, while Section 49 of the Bill provides that it will be lawful for material that has come from a person's body (alive or dead) in the course of treatment, diagnostic testing or whilst participating in research that has ceased to be used or stored for use for a purpose specified in Schedule I to be dealt with as waste – the legislation still does not make clear what the status of this 'waste' will be. If it were to be declared res nullius then it could become lawfully available for use for purposes within or outwith Schedule1. However, as it is currently drafted, Schedule I activities appear to remain prohibited notwithstanding that the material has been officially declared to be waste.

The Status and Use of 'Technological Artifacts': Prohibition of Commercial Dealings

The broad definition of 'relevant material' that is applied generally in the Act "material, other than gametes, which consists of, or includes human cells" is so all encompassing that a series of different exceptions had to be made to it in order to render the Bill operable. In Section One of the Bill, which addresses the removal, storage and use of such material, several exceptions are made to the general definition of relevant material: for embryos outside of the body (as they are dealt with under separate legislation), but also for hair and nail from the body of a living person. Some queries have been raised about the raison d'etre behind these latter exceptions. While both are evidently necessary to prevent criminalisation of unproblematic domestic acts such as cutting and retaining nail and hair they also create an inconsistency in that both, but hair in particular, while consisting of acellular keratin for most of it length,

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nonetheless contains cells at the root tip. At present these cells could presumably be used for all of the purposes in Schedule One without consent, even though consent provisions would normally apply if the material was not excepted. Given this, we might question the logic of this exception, or the every least its practicability in application. As an entire hair will certainly 'include human cells', it may well be asked whether the cells at the root of the hair are included or excluded material for the purposes of the definition, or at what point along the axis of the hair the exception come into force?

The exceptions that are made in Section One to the definition of relevant bodily material are not, however, consistently applied. They are withdrawn in Sections 50 (5) and Schedule 5 that deal with DNA analysis for obvious reasons, as hair follicles are, for example, a prime source of DNA; and added to in the Section 32 which relates to the Prohibition of Commercial Dealings in Human Material. This episodic and ad-hoc revision of basic definitions on a section-by-section basis exemplifies the difficulty that the drafters have had in trying to accommodate the very different relationships that different constituencies have to bodily materials when in different forms. So, for example, while it is clear that the drafters have no wish to insist that wigmakers obtain consent from every individual from whom they source hair, they also recognise that they must carefully control those who wish to access the very same materials for the purposes on non-consensual genetic testing – such as paternity testing. Relying on the rather crude mechanism of definitional changes provides one means of accomplishing this work however it comes with an attendant risk of confusing practitioners and making them very uncertain as to what uses they may lawfully make of what materials, in what circumstances.

This variability in the application of the definition may also give rise to further difficulties – perhaps even a loss of public confidence in the ability of the Bill to regulate activities that the public find objectionable or unacceptable. One of the most consistent findings to emerge from a series of recent public consultations was the abhorrence with which members of the general public view the practice of commercialising the use of human organs or tissues or of dealing in them for profit. The Bill, in dealing with these issues, creates new offences in relationship to the supply and use of whole bodies and 'relevant bodily materials' for profit – in effect – for reward beyond the cost of supply – however it creates exceptions for several categories of these relevant bodily materials. These include on this occasion: gametes, embryos, hair and nail from the body of a living person, and, a notable other: "material which is the subject of property because of an application of human skill".

Under Section 59 (7) of the amended Bill, which deals with general interpretation, we find another curious, but related, exception. It is here stated that: "For the purposes of this Act, material shall not be regarded as from a human body if it is created outside the human body". An explanation for the apparently tautological nature of this statement can be found in the explanatory notes that accompany the Bill. They give a fuller exposition of what this exemption might mean in practice, noting that "cell lines are also excluded by virtue of clause 59(7), as is any other human material created outside the human body". The intention of the Bill here is clear. In this

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biotechnological age, human organs and tissue are often processed in quite complex ways, many of which demand the investment of considerable work and skill. The Bill anticipates that those 'technological artifacts' that are created from relevant bodily material must be excepted from regulation under this Bill as they are likely to be claimed as a form of property by the scientists or technicians that have applied their skill in their manufacture.

It is by no means clear, however, how these sections of the Bill will be interpreted by the new Human Tissue Authority – the agency charged with responsibility for overseeing the implementation of the Act. While it is likely that the Authority may look to the common law for guidance on the question of how much – or how little – skill or invested technical labour must be applied to human tissue to make it the subject of property, they are unlikely to find an unambiguous answer there. The existing case law Doodeward v Spence; Dobson v North Tyneside Health Authority; and R. Vs Kelly; has historically, as Grubb has noted, been even less persuasive of any settled position than has legislation.[16]

It could be argued that highly characterized collections of especially prepared organs fixed in formalin; mounted sections of tissue; or especially selected, stained and mounted collections of histopathological slides that relate to a specific disease condition; may all constitute 'works' or technological artifacts that are the product of the investment of a considerable degree of highly specialized technical labour. In which case, pathologists could rightfully apply for them to be exempted from the regulation governing commercial dealings in human materials under Section 32 (9) of the Bill on the grounds that they constitute their personal property. This may well be an entirely appropriate reflection in law of the way in which relationships to biological materials must be re-cast as the materials themselves are re-made into new, collectively constructed objects in which many parties may have rights or interests.
It is not clear however, that the basis for extending this right, or the limitations of the right will be immediately evident, or embraced, by those whose tissue is employed in their manufacture.

If, as stated, a key purpose of the Bill is to inject clarity into the law relating to the uses of archived human tissue, it is unfortunate that it has left this matter so ill-determined in the legislation as it currently stands .The Bill does not establish, for example, whether the fixing of specimens or the production of slides (or both) would constitute an input of sufficient work and skill to warrant the grant of extra rights in relation to these objects, and indeed, whether those rights would be merely rights of lawful possession or if they might be proprietary rights. On March the 26th this year Mr. Justice Gage handed down his judgment in the Nationwide Organ Group Litigation case - an action bought by parents of children whose organs were retained at Bristol and Alder Hey hospitals to establish whether the defendant hospitals had, in so doing, committed the tort of wrongful interference with a body; were negligent; and had breached Article 8 of the Human Rights Act.[17] It is interesting to note that he determined that in cases where body parts had been retained following a coroners' post-mortem examination that there were no grounds for sustaining a tort of wrongful interference with the body as the claimants had no right of burial and possession of

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organs lawfully removed and retained at a coroner's post-mortem, and that, moreover, the application of work and skill that had been applied to retained organs during the post-mortem and histopathological process was sufficient to entitle the hospitals to lawful possession of the organs, as property.

He determines at Section 148 for example, that "In my judgment the principle that part of a body may acquire the character of property which can be the subject of rights of possession and ownership is now part of our law. In particular, in my opinion, Kelly's case establishes the exception to the rule that there is no property in a corpse where part of the body has been the subject of the application of skill such as dissection or preservation techniques. The evidence in the lead cases shows that to dissect and fix an organ from a child's body requires work and a great deal of skill, the more so in the case of a very small baby such as Rosina Harris. The subsequent production of blocks and slides is also a skilful operation requiring work and expertise of trained scientists." He goes on to state unequivocally at 160 that: "For the avoidance of doubt, in my opinion, in the three lead cases the evidence of the pathologists shows that the work and skill applied to the parts of the body removed at the post-mortem is sufficient to come within the Doodeward exception. They are therefore capable of being subject to rights of possession", and crucially at 257 that 'in my opinion, following the post-mortem, the hospital acquired proprietary and possessory rights to the organs (my italics). The question that remains is how the new provisions of the Human Tissue Bill can or will be interpreted in light of this judgment and what the implications of that interpretation might be? It is unfortunate that this issue has not been discussed or resolved in the drafting of the new Bill as it will undoubtedly become more pressing in years to come and may well be the subject of further litigation.

A final, but potentially equally contentious issue that may attract further attention is the exception that has been made at 59(7) for material from a human body that is created outside the human body. While this exemption is designed to place technologically produced human materials – such as cloned cells and cell lines beyond the jurisdictional reach of the Bill, it is not clear that there will be widespread public support for exempting materials that are derived from the human body (such as human cells) simply because they are produced by a technological process. If the general public consider it unacceptable to profit from a commercial use of a person's cells they are unlikely to agree that it is acceptable to profit from the use of their cloned cells. The furore and legal battles that have surrounded the commercialisation of the HeLa and Mo cell lines in the US suggest that individuals may continue to believe that they have interests in their bodily materials, even when reproduced through a technological process. If the exception is being made on the basis that they constitute a technological work produced through the applied skill and work of a specialized technician then, in the interests of consistency and clarity, it might be best if any exception be made on this basis alone.

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Conclusion

The new Human Tissue Bill provides a timely revision of the existing Human Tissue Act of 1961 and offers a much more comprehensive regulatory framework for the retention, storage, and use of human tissue in the UK than has been available to date. Following a number of very significant recent amendments to the Bill there is every reason to be hopeful that it will meet its stated goal of balancing the rights and expectations of individuals with those of practitioners involved in providing research, education, training, pathological and public health surveillance services to the population as a whole. However several further revisions may yet provide remedies for some remaining, but significant anomalies. The first revision would make clear that reversible and linked anonymisation would be permitted, particularly in general epidemiological research. The second would ensure that all forms of education or training whether related to research or human health would be able to be undertaken on remnant tissue derived from living persons without their explicit consent. The third would allow for the provisions for anonymity in the use of tissues from living persons to be waived in certain specific circumstances (for example, when a clinician would wish to conduct research on a patient group known to him or her), if undertaken with appropriate ethical approval. Finally, the drafters may wish to re-examine the basis of some exceptions: those for hair; for material which is the subject of property because of an application of human skill; and for material created outside the human body, to consider whether they are fully operable or necessary and whether the Bill might benefit further from tightening, clarifying or even expunging those that serve to obfuscate understanding or implementation of the Bill as it currently stands.

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[10] Professor Peter Furness is a diagnostic histopathologist working at the University Hospitals of Leicester and is a member of council of the Royal College of Pathologists

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Public Policy and the Future of Bioethics[1]

ALASTAIR V. CAMPBELL

Abstract

This highly speculative paper seeks to discern where the discipline of Bioethics may be heading in the next decade or two. It is clear that the rapid pace of scientific discovery and technological innovation will not slacken, and, as a result, fresh moral issues, for which there are no precedents in currently accepted moral wisdom, will rapidly emerge. This mushrooming of ethical problems will be taking place at a time of increasing moral pluralism, when common moral values become harder to establish, and powerful subgroups embrace moral dogmatism, whether religious or secular in character.

Faced with such complexity and confusion, governments and industrial groups will increasingly seek guidance from bioethics "experts", through paid consultancies, advisory panels and commissioned reports on specific topics. But Bioethics itself is currently in a stage of flux: 1. Certain research areas in Bioethics have 'bolted' (in the horticultural sense), because of a rich injection of funds – notably genetics and stem cell research – while other areas are relatively under-researched. 2. Inter-disciplinarity has become *de rigueur*, largely under funder pressure, and, allied to this, an insistence on empirical work has created conceptual confusions. 3. There is a continuing ferment in bioethical theory, with little sign of productive co-operation between rival camps. Indeed theoretical enrichment seems to lag far behind the constant demand for relevance and 'applied ethics'.

So what of the future? I detect certain trends, some to be deplored and discouraged, others to be applauded and nurtured. On my 'black list' are: the commercialisation of Bioethics; and the dumbing down of several critical disciplines in the name of relevance. On my 'white list' are: further adventures in theory; inter-disciplinarity come of age; and the future envisioned in today's young minds.

Introduction

It has become a platitude to say that the speed of scientific and technological innovation has outstripped our shared moral visions, but it is nonetheless true. Some controversies are too obvious too ignore – the debates over cloning, uses of embryonic stem cells, environmental protection, climate change, or GM foods, are all obvious examples. But many more exist in reality or potential. A good example would be the possibility of

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sperm derived from adult stem cells (already achieved in mice), which would revolutionise our understanding of parenthood as the joint enterprise of male and female. If this future becomes an actuality, any woman could have sperm customised from herself or another woman in order to achieve a pregnancy, without any male source whatsoever. Faced with this cascade of new dilemmas governments turn to 'experts' to rescue them from the accusation of doing nothing. As a result we have an increasing number of panels, commissions, consultants and, from them, a mountain of reports (many of them gathering dust in government offices). Bioethics is now highly topical and popular, and scarcely a day goes by without someone making the claim to ethical expertise in some field. The question is, does the discipline of Bioethics really have anything to offer to those who must decide public policy?

The Inevitablist Critique

To answer this, I must first respond to a common critique of the relevance of reasoned bioethical debate. To coin a particularly horrible neologism, I call this the "inevitablist" critique. It runs as follows; people have always worried about change and seen it as morally problematic. But history shows that sooner or later what is regarded today as morally unfortunate will become commonplace and fully acceptable tomorrow. We cannot stem the flow of scientific "progress" with arguments about morality. Since change is inevitable, so we must simply learn to accept it. A favourite example for this position is the powerful opposition to assisted conception when it was first introduced some decades ago, yet now, it is argued, everyone applauds these methods of overcoming fertility. So, the conclusion runs, we may as well accept that today's "yuk factor" is tomorrow's social acceptance, and not waste time in analysing the moral desirability of what will happen in any case.

This argument cannot of course be directly refuted, since it contains a prediction about the future, which cannot be conclusively proved or disproved in the present. But we can point to its simplistic historical analysis: assisted reproduction, for example, far from being seen as simple scientific progress with no moral problems, is now being perceived as highly complex morally and in need of careful regulation. As the stem cell controversy increases, many countries look with envy to the UK, where the careful discussion of the Warnock Report has led to a fully regulated system, allowing both control of extremes and flexibility when new issues arise. Such a moderated approach is much more difficult in countries where there are no mediating structures between vacillating public opinion and political expediency. The confused policy in the USA regarding embryonic stem cells provides an excellent illustration of this. In this, as in many other areas of technical innovation, it is certainly possible to channel, if not to halt completely, the flow of change. It is surely the task of a well informed and carefully reasoned Bioethics to guide the policy makers. But is the discipline up to the task? In the next section I look at the problems we face at the present time in the discipline.

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Bioethics in Flux

As I see it, there are three problem areas in the discipline of Bioethics at the present time, if policy makers are going to look to it for guidance: 1. Uneven growth; 2. Disciplinary confusion; and 3. Ferment in theory.

Uneven Growth. Bioethics has had a curious history. Its origins can be traced to the emergence of a counter culture to scientific medicine in the 1960s, which questioned the ability of doctors alone to deal with the ethical issues arising in practice. Partly welcomed by the profession and partly feared by it, this new style medical ethics focussed on issues like medical research and treatment decisions, seeking help from a range of disciplines, such as theology, philosophy, law and social science. It became increasingly clear that many of the new problems in the area of human health and welfare lay outside the professional practice of doctors and encompassed a range of other scientific disciplines, including epidemiology, genetics, biochemistry, pharmacology and environmental science.

As this expansion has increased, certain areas have 'bolted', nurtured by an over rich source of nutrients. The acronym ELSA (ethical, legal and social aspects), first used in the Human Genome Project, soon became the signal for the injection of cash of a scale quite unknown before to many of the humanities based researchers in Bioethics. Two areas are particularly noted for such generous funding: genetics and stem cell research. So political priorities have begun to define the priorities of research in Bioethics. Of course these are both highly important areas, in which excellent work has been and will be done, but the danger is obvious - we may starve of nourishment other areas of the discipline, perhaps especially those which are more critical of current political agendas and which take a more sceptical view of the values of science and technology. I have in mind issues to do with world hunger, injustice in health care distribution, threats to our environment, the rising tide of mental illness and the dilemmas of ageing (to take just a few examples).

The Fashion for Interdisciplinarity. The second problem area is also potentially the greatest strength of Bioethics – the current fashion for interdisciplinary work. This fashion has been partly created by the funders, notably the Wellcome Trust and the European Commission, but increasingly also by UK government funders, for example, the recent Stem Cells Initiative launched jointly by the MRC and ESRC. As I pointed out earlier, a mix of disciplines has been a characteristic of the field since the early days of the new medical ethics, but as the years go on, some serious problems have emerged. Firstly, it is very difficult to retain the academic integrity of a discipline, when research is crossing a number of disciplinary boundaries. There is a risk is a "dumbing down", a loss of rigour and complexity, in the process of trying to communicate with scholars who use an entirely different discourse. Secondly, it is likely that "blue skies" research in the component disciplines of Bioethics will suffer, when all the priority is put on getting

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disciplines together to produce relevant reports. Thirdly - and to my mind the most serious issue –there is the risk that the relationship between theoretical and empirical work in Bioethics is not carefully enough articulated. (I shall return to this issue later).

Ferment in Theory. Thirdly, Bioethics may not be able to meet the demands of policy makers because of the current ferment in theoretical approaches. We are past, I trust, the naïve idea that with four cardinal principles all problems can be solved! The European dimension has given us terms like solidarity, integrity, and dignity, but with a continuing debate about their meaning and application. At the same time the whole philosophical approach based on structures, obligations, or principles has been effectively challenged by feminist theory, by narrative ethics and by a rediscovery of virtue ethics. I do not deplore this diversity – it is a sign of a healthy discipline with a stimulating internal critique - but it does make the demand from outside for ethical "expertise" more problematic! Which Bioethics "expert" is the right expert? How are the politicians to decide?

The Future of Bioethics

So what of the future? I am a Celt – part Scottish part Irish – but I do not possess the Second Sight! I can merely try to detect trends. I have a black list and a white list. I believe we must eliminate the former and nurture the latter.

The Black List

A. Selling the Soul of Bioethics. What of the ethics of Bioethicists? With the increasing popularity of Bioethics in areas of massive commercial gain there comes the risk of corruption. Awareness of this has begun to emerge in the USA. - I am thinking here of the courageous writing of Carl Elliott about the hiring of Bioethics consultants, without their special connection with the commercial organisation being declared in publications.[2] I do not know whether such a problem exists in the UK or elsewhere in the world, but it seems likely that it will sooner or later. The danger is already well known in science and medicine generally, and it will become essential to define at an early stage the acceptable rules of conduct by those claiming Bioethics expertise. A related problem, is the increasing tendency to appoint one person to give the ethical dimension in an advisory group. Given the healthy diversity of bioethical theory, this must be resisted, and at least two places should be allocated to allow a proper debate to be held. We should never hunt alone!!

B. Pop Bioethics. A second item on the black list is the naïve use of surveys of public opinion to establish ethical norms. To philosophers this is the familiar problem of the Naturalistic Fallacy. Surveys of opinion on contentious ethical topics no doubt have a value in identifying areas of social agreement or disagreement, but they cannot be a

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substitute for reasoned argument about the alternatives open to policy makers. To take a topical example, the decision of the HFEA to allow embryo selection to produce a "savour sibling" was a popular one with the British public, who reacted to the strong appeal of the tragedy confronting the parents of children with potentially fatal disorders. But the issue, which the Authority had to resolve, was whether it was morally right to create a child as a means of saving the life of another. Their decision to authorise the procedure was based on a careful analysis of this moral question, as it should have been. Naturally their conclusion remains ethically contentious, because such decisions raise wider questions of how we view children in our society.

The White List.

The "white list" is potentially a long one, since the range of possibilities for reasoned bioethical debate keeps expanding. But out of the range, I would draw attention to three areas I believe must be strongly nurtured: further adventures in theory; a mature account of interdisciplinarity; and a focus on youth.

A. Further Adventures in Theory Beauchamp and Childress's *Principles of Biomedical Ethics* has had a huge influence on a whole generation of researchers and practitioners, but the time is overdue for fresh incursions into the theory underlying Bioethics. We have to escape from the swamp of relevance for a while and look again at the underpinning of bioethical debate. I have already mentioned the need for "blue skies" research, and if this can be encouraged, then there should be a new generation of scholars who will revisit the nature of moral theory in this applied field. Just what shape this theory will take it is too early to say, but it will have to be based on a full understanding of the latest developments in moral theory as a whole. The old debates are looking somewhat tired and out of date!

B. Interdisciplinarity Come of Age There are already real signs of more nuanced writing on the relationship between ethics and the social sciences. I hope we have got beyond the insulting idea that social scientists "scoop facts" for ethicists to work on! Instead we have several models of how empirical findings might relate to ethical assertions. Two very notable recent contributions in this area are the EU funded EMPIRE project, edited by Soren Holm and Monique Jonas[3] and an article by Erica Haimes on the contribution of the social sciences to ethics.[4] Holm and Jonas survey possible models, ranging from a pure application of theory to practical applications, through the "reflective equilibrium" model, to models based on consistency between current beliefs and theoretical critique. The latter models are perhaps of special interest in view of a revival of scholarship in Aristotelian ethics, which blends accepted custom with philosophical analysis. Such an approach takes us beyond the "naturalistic fallacy". Similar issues arise from the careful assessment by Haimes of the state of play between ethics and social science. The main force of her paper is to show that social theory is beyond its positivistic phase and that the tension between

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fact and value in the social sciences has its counterpart in current debates in ethics. Both of these writings show that interdisciplinarity may be "coming of age", allowing some exciting new collaborations to take place between the disciplines interested in Bioethics at a theoretical level, not merely at a practical one.

C. Focus on Youth My last "white list" item" is the challenge that some Bioethics scholars are taking up to communicate with the younger generation, correctly perceiving that many of the possibilities we debate today will be realities in their world. For some years the Danish Council on Ethics has run a parallel programme to their council meetings, engaging young people in coming up with recommendations on the issues being discussed. In my own Centre, we are about to embark on some research which will enable children aged 12-14 to be trained as a research ethics committee and then to discuss actual protocols in tandem with the actual committee dealing with them. This was based on our experience running a project, which involved nine to eleven year olds discussing the ethics of research participation, including the taking and storage of DNA samples. It made us realise that in our interdisciplinarity we have left out the educationalists, a major deficit. These children were interested and articulate, and perfectly able to think through the dilemmas of consent and confidentiality.

The Future is Now

Such attempts to move Bioethics from the academic cloister, or the government committee room, to the fresh world of young people's moral perceptions raise real hopes for the future of Bioethics. The dangers noted earlier – of "pop bioethics" and of "dumbing down" of theory - are of course obvious in these experiments. But neither is inevitable if this exercise in education is done in a sophisticated way and is properly evaluated. And if bioethics is to avoid the perils of corruption by commerce and government, and of a confusion of moral value with public opinion, then its future lies in the education of those people for whom today's looming dilemmas will be tomorrow's reality.

The future is now!

[1] Modified version of a paper given to the Cardiff Centre for Ethics, Law and Society on 12th June 2004.
[2] C. Elliott. Taking Money from the Drug Industry: The Rules Tighten. The Hastings Center Report 2003; 33:4, C. Elliott. Diary: the Ethics of Bioethics. The London Review of Books 2002: 24 (23): 36-37.
[3] S. Holm and M.F. Jonas. 2004. Engaging the World: The Use of Empirical Research in Bioethics and the Regulation of Biotechnology. Amsterdam. IOS Press.
[4] E. Haimes. What Can the Social Sciences Contribute to the Study of Ethics? Bioethics 2002; 16(2) : 89-113.

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