Appendices and Acknowledgements

Appendix 1

Moore v Regents of the University of California

1 The judgment of the Supreme Court of California on the preliminary legal issues was given in 1990.[1] Panelli J in his judgment summarised the facts as follows:

> *"Moore first visited UCLA Medical Center on October 5, 1976, shortly after he learned that he had hairy-cell leukaemia. After hospitalizing Moore and "withdr[awing] extensiveamounts of blood, bone marrow aspirate, and other bodily substances", Golde confirmed that diagnosis. At this time all defendants, including Golde, were aware that "certain blood products and blood components were of great value in a number of commercial and scientific efforts" and that access to a patient whose blood contained these substances would provide "competitive, commercial, and scientific advantages."*
>
> *On October 8, 1976, Golde recommended that Moore's spleen be removed. Golde informed Moore "that he had reason to fear for his life, and that the proposed splenectomy operation . . . was necessary to slow down the progress of his disease." Based upon Golde's representations, Moore signed a written consent form authorizing the splenectomy.*
>
> *Before the operation, Golde and Quan "formed the intent and made arrangements to obtain portions of [Moore's] spleen following its removal" and to take them to a separate research unit. Golde gave written instructions to this effect on October 18 and 19, 1976. These research activities "were not intended to have . . . any relation to [Moore's] medical . . . care." However, neither Golde nor Quan informed Moore of their plans to conduct this research or requested his permission. Surgeons at UCLA Medical Center, whom the complaint does not name as defendants, removed Moore's spleen on October 20, 1976.*
>
> *Moore returned to the UCLA Medical Center several times between November 1976 and September 1983. He did so at Golde's direction and based upon representations "that such visits were necessary and required for his health and well-being, and based upon the trust inherent in and by virtue of the physician-patient relationship. . . ." On each of these visits Golde withdrew additional samples of "blood, blood serum, skin, bone marrow aspirate, and sperm." On each occasion Moore travelled to the UCLA Medical Center from his home in Seattle because he had been told that the procedures were to be performed only there and only under Golde's direction.*

[1] *Moore v Regents of the University of California* (1990) 793 P 2d 479

"In fact, [however], throughout the period of time that [Moore] was under [Golde's] care and treatment, . . . the defendants were actively involved in a number of activities which they concealed from [Moore]. . . . Specifically, defendants were conducting research on Moore's cells and planned to "benefit financially and competitively . . . [by exploiting the cells] and [their] exclusive access to [the cells] by virtue of [Golde's] on-going physician-patient relationship. . . ."

Sometime before August 1979, Golde established a cell line from Moore's T-lymphocytes. On January 30, 1981, the Regents applied for a patent on the cell line, listing Golde and Quan as inventors. "[B]y virtue of an established policy . . . [the] Regents, Golde and Quan would share in any royalties or profits . . . arising out of [the] patent." The patent issued on March 20, 1984, naming Golde and Quan as the inventors of the cell line and the Regents as the assignee of the patent (US Patent No 4,438,032 (Mar 20, 1984).)

The Regent's patent also covers various methods for using the cell line to produce lymphokines. Moore admits in his complaint that "the true clinical potential of each of the lymphokines . . . [is] difficult to predict, [but] . . . competing commercial firms in these relevant fields have published reports on biotechnology industry periodicals predicting a potential market of approximately $3.01 Billion Dollars by the year 1990 for a whole range of [such lymphokines]. . . ."

With the Regents' assistance, Golde negotiated agreements for commercial development of the cell line and products to be derived from it. Under an agreement with Genetics Institute, Golde "became a paid consultant" and "acquired the rights to 75,000 shares of common stock." Genetics Institute also agreed to pay Golde and the Regents "at least $330,000 over three years, including a pro-rata share of [Golde's] salary and fringe benefits, in exchange for . . . exclusive access to the materials and research performed" on the cell line and products derived from it. On June 4, 1982, Sandoz "was added to the agreement," and compensation payable to Golde and the Regents was increased by $110,000. "[T]hroughout this period, . . . Quan spent as much as 70 [percent] of her time working for [the] Regents on research" related to the cell line.

2 Moore initially filed suit in 1984 in the California Superior Court against Golde, Quan, the Regents of the University of California, Sandoz, and Genetics Institute. Moore alleged that he had a cause of action in conversion (wrongful interference with another's property) and for lack of informed consent. The case passed from the Superior Court to the California Court of Appeal and then to the Supreme Court of California. The majority of the Supreme Court decided that Moore had no property rights in cells taken from his body, but remitted for trial the issue of whether the doctors had been in breach of the duty to obtain Moore's informed consent and of the duty of loyalty to the Moore as their patient.[1] The case was subsequently settled out of court.

Appendix 2

The report of the Health Council of the Netherlands : *Proper use of human tissue*[1]

1 The report of the Health Council of the Netherlands on the **Proper use of human tissue** "*formulated a number of principles to be observed in the further use of human tissue:*

1 The intended use must be morally acceptable in so far as its purpose is to promote human health.

2 Human tissue should always be used with the greatest of care.

3 The relationship between patient and doctor must not be undermined by the use of bodily material. The patient must rest safe in the knowledge that his or her own needs will continue to come first. The doctor should exercise openness regarding the storage and use of human tissue and must duly inform the patient thereof.

4 People cannot be forced to co-operate with the use of material obtained from them, even if it is in a good cause.

5 The privacy of those whose material is put to further use must be respected and protected.

6 The Committee endorses the principle of non-commercialism which applies to donation and extends this principle to the collection of human tissue in general. Such material should not be handed over or transferred to a third party by anyone whomsoever (whether patient, donor, doctor or institution) with a view to making profit."

2 These principles are broadly consistent with our arguments and conclusions. We would have some marginal reservations. The fourth principle we have found difficult to interpret: if it applies to tissue removed during treatment, then in some circumstances we disagree (paragraphs 13.12, 13.26). The fifth principle invokes the concept of 'privacy', which is difficult to define in UK law and practice: nevertheless our report makes the same points, we think, in terms of confidentiality (paragraph 13.33).

[1] Health Council of the Netherlands (1994) **Proper Use of Human Tissue** Publication N° 1994/01E The Hague

3 The policy recommendations of the Health Council's report are as follows. The partial contrast with the conclusions and recommendations of this report illuminates our arguments and offers the readers an opportunity to judge their force. The Health Council's *"recommendations concerning the acquisition, storage and use of human tissue are designed to ensure that:*

1 institutions provide patients with general information concerning the storage and use of human tissue;

2 human tissue is donated or transferred to a third party without gain;

3 no more material is obtained than is necessary for the purpose originally intended;

4 material is not stored without a good reason;

5 such material is managed carefully and safely;

6 identifiable material, if stored, is given a number or code (ie coded);

7 institutions regulate the management of human tissue;

8 there is an administrator responsible for ensuring compliance with the rules;

9 non-identifiable material is used wherever possible in preference to identifiable or indirectly identifiable material;

10 the person concerned is given the opportunity to object to the further use of non-identifiable material;

11 the consent of the person concerned is sought for the storage (and subsequent use) of identifiable material for reasons other than that originally intended;

12 one is reserved in storage (and subsequent use) of material from persons who are not competent to give consent, for reasons other than that originally intended;

13 material supplied to third parties is either non-identifiable or only indirectly identifiable;

14 the advice of medical ethics committees is sought, where necessary."

Mechanisms for controlling the further use of human tissue

4 The Health Council's report identifies the role of patients' consent as a mechanism for the control of the further use of tissue. We have not placed the same emphasis on patients' consent as a possible control on the further use of human tissue removed during treatment. Consider the problems that would arise if a patient demanded the return of removed tissues. In fact good medical practice requires the archiving of

tissue for continuing therapy and medical audit. It seems to us inadvisable to hold out a possibility, however theoretical, that ought to be denied as a matter of proper medical practice. Second, there is a practical problem with patient consent as a control: patients are often difficult to trace even only one year after treatment and over a lengthy period of time the proportion that cannot be traced increases greatly.

5 Nevertheless, we are at one with the Health Council's report in thinking that there should be a clear mechanism or set of mechanisms controlling the further use of human tissue. This, as we see it, is the role of the medical intermediary. The medical intermediary, whether it be the pathologist archiving tissue or the medical professional in charge of a tissue bank, works within the framework of law and of professional codes of conduct. In English common law the professional code of conduct has traditionally been accorded the backing of the courts. We see such intermediaries as the proper custodians both of patient's rightful expectations of tissue being treated with appropriate dignity and respect and of the patients' rights to confidentiality. We have indicated also the role of medical intermediaries in providing a barrier to profit-making in the procurement and supply of human tissue (paragraphs 6.38 - 6.40).

6 In the UK, medical intermediaries are already well established in the role that we attribute to them in controlling the further use of human tissue. They operate under professional codes of conduct that can be fairly rapidly adapted to new developments. Our recommendations, if they are accepted, should lead to a greater consistency and tightness in the control mechanism.

Balance between the public good and individual patient wishes

7 The Health Council's report emphasises individual patient wishes. We have attempted to pay attention to what seem to us the balancing considerations of the potential for public benefit. The availability of archived tissue, not only for medical audit but also for epidemiological research, works both for the benefit of individual patients and for the public good. Indeed in our view, to insist on the availability of tissue removed during treatment for medical audit and for further medical and scientific uses does more for the real rights of patients than providing for the wishes of a patient who might wish for tissue not to be archived. In practice, however, we would hope that there would not be such a great difference between the two sets of recommendations. For our own proposals are designed to protect patients' rights while ensuring the necessary availability of tissue for therapeutic ends. We would emphasise that only a small proportion of tissue is used for anything but the therapy of the original source.

Appendix 3

Human tissue used in transfusion, transplantation or reconstructive surgery

Amnion

Blood and blood components

Blood vessels

Bone chips and bone segments

Bone marrow

Cornea

Dura mater

Fallopian tube

Fascia lata

Fetal serum

Fetal tissues or cultures, for example
thymus, liver, pituitary, brain

Fibroblast cultures

Heart valves

Intestines

Islets of Langerhans

Organs, for example kidneys, heart, lungs,
liver, spleen, pancreas

Ossicles

Ova, embryos

Semen

Skin

Tendons

Trachea

Appendix 4

Therapeutic and research products derived from human tissue

This list offers examples and is not intended to be exhaustive. Some of these products may be derived both from human tissue and by alternative methods involving recombinant DNA technology, cell culture or the use of animals.

Blood and blood products

Whole blood
Serum albumin
Fibrinolytic drugs: urokinase, tissue-type plasminogen activator, antistreplase
Anti-fibrinolytic drugs: aprotinin, Factor VIII, Factor IX, Factor XI.

Immunological products

Normal human immunoglobulin
Specific immunoglobulins: tetanus, hepatitis B, rabies, varicella-zoster, anti-D(Rh_0).

Monoclonal antibodies

Examples of monoclonal antibodies are IgM antibody to E.coli endotoxin and radiodiagnostic antibodies to tumour antigen and myosin

Endocrine Agents

Insulin
Thyroid hormone
Parathyroid hormone: calcitonin
Cortisone
Male and female sex hormones
Hypothalamic hormones: gonadorelin, protirelin, sermorelin
Anterior Pituitary hormones:
corticotrophin replaced by tetracosactrin,
growth hormone replaced by somatotropin,
chorionic gonadotrophin, menotrophin, urofollitrophin.
Posterior pituitary hormones: vasopressin (analogues lypressin, desmopressin), oxytocin.

Exocrine Agents

Prostaglandins

Cytokines: interferon, erythropoetin, interleukins, colony stimulating factors, tumour necrosis factors, transforming growth factors

Structural Products

Collagen

Hyaluronic acid

Dura preparations

Products for Somatic Cell Therapy

Hepatocytes, myoblasts or pancreatic islet cells for implantation

Cells for implantion as an in-vivo source of a therapeutic product such as an enzyme, cytokine or coagulation factor

Activated lymphoid cells such as lymphokine activated killer cells and tumour-infiltrating lymphocytes for infusion

Products for Somatic Cell Gene Therapy

Cells modified ex-vivo by addition of genetic material to correct a genetic disorder such as adenosine deaminase deficiency (ADA), or cystic fibrosis.

Future techniques may include direct administration to patients of retroviral or other vectors to alter genetic content of cell.

Research Products derived from Human Tissue

Human cell lines

Genomic DNA libraries, cDNA libraries, purified RNA, Southern blots of genomic DNA and Northern blots of poly A+ RNA. These products may be derived from a variety of human adult, infant and fetal tissues (for example, placenta, adrenal gland, aorta, bone marrow, intestine, fibroblast, breast, eye, ovary, prostate, thymus, stomach, trachea, testis, heart, brain, pancreas, lung, kidney, skin, liver).

Appendix 5

Strategies for tissue replacement

Many of these examples are still in the process of development and are not yet used therapeutically.

1 Nervous system

- Fetal dopamine producing cells used to treat Parkinson's disease
- Dopamine releasing immortalised cell lines encapsulated in polymer membranes
- Encephalin and catecholamine releasing cell implants used in relief of pain
- Autologous bridging nerve grafts with synthetic guiding conduits; acceleration by Schwann cells seeded to polymer membranes

2 Cornea

- Corneal epithelial cells pre-seeded on polyvinyl alcohol hydrogels

3 Skin and other wounded tissues

- Composites of silicon, and chondroitin sulphate and collagen to induce new blood vessel formation and connective tissue growth in dermis
- Culture of keratinocytes in irradiated fibroblasts to produce large grafts
  Human neonatal dermal fibroblasts grown on degradable polyglycolic acid mesh
- Fibroblasts placed on hydrated collagen gel

4 Liver

- Suspensions of hepatocytes encapsulated in microcapsules or hollow fibres attached to polymer networks

5 Pancreas

- Pancreatic islets encapsulated in membrane

6 Cartilage, bone and muscle

- Collagen-glycosaminoglycan templates, isolated chondrocytes, chondrocytes attached to natural or synthetic polymers
- Bone morphogenic proteins, transforming growth factor
- Cells grown on synthetic polymers or ceramics
- Myoblast transfer

7 Blood vessels and cells

- Polymers with cell adhesin ligands lined with endothelial cells
- Cell free haemoglobin
- Platelet proteins encapsulated in lipid vesicles
- Bone marrow stem cells and specific inducers

Appendix 6

Guidance for the referral of proposals for research on human tissue to research ethics committees

1 Research proposals involving human subjects, material or records and taking place broadly within the NHS are submitted for approval to a Local Research Ethics Committee (LREC) administered by the District Health Authority.[1] The Medical Research Council, medical research charities and private-sector companies may also refer proposals to LRECs or to a variety of other research ethics committees including, for example, the Royal College of General Practitioners' Clinical Research Ethics Committee.

2 Where there is any doubt whatsoever in the mind of the research investigator or collaborators on the ethics or propriety of the research to be undertaken, recourse to a research ethics committee is advised. This will be particularly important in instances where the relationship between research investigator and subject, whether patient or healthy volunteer, is close and trusting.

3 The guidance offered by the Working Party for referral to research ethics committees of research proposals involving the removal of human tissue from patients or volunteers is to refer those programmes:

1 that require the identity of patients and healthy volunteers to be made known to the research investigator even if the research is retrospective and the tissue has been stored or archived;

2 that require prospective collection of tissue over and above that strictly necessitated by diagnosis or treatment of disease. Here, the specific consent of the subject to the research procedure must be secured. This applies to all studies on healthy volunteers;

3 where research is of an unusual or essentially innovative nature, particularly where this may lead or is intended to lead to commercial or therapeutic developments, or may have implications that could arouse public concern;

4 where handling charges or fees in respect of tissue are to be paid to the person supplying the tissue or that person's institution or employer;

[1] Department of Health (1991) **Local research ethics committees** London

5 where any research will, may, or is intended to lead to therapy involving the use of autologous or heterologous transplantation, transfusion or other transfer between human beings, living or dead;

6 where research may lead to or presage alteration of germ cells or lines;

7 that involve any research on the human fetus or embryo, except that on left-over tissue (see 4.2 below).

4 Thus, the advice of research ethics committees should be sought in connection with almost all research involving human tissue, **subject to the following exceptions**:

1 research use of anonymised left-over tissue. Such tissue is ordinarily removed by surgeons or pathologists who are not closely involved with the proposed research. Even where this is not the case, provided that no more tissue has been taken than is required in the necessary course of diagnosis or treatment, recourse to a research ethics committee is not required;

2 research use of anonymised tissue left over from investigations or treatment of the fetus *in utero*, subject to the provisos outlined in paragraph 3.2 above;

3 use of anonymised left-over tissue in the course of developing technology, or implementation of quality control or assurance programmes;

4 review of anonymised archived material from any source;

5 DNA extraction from left-over or archived tissue where anonymity is assured, or the procedure is in furtherance of diagnosis or preventive medicine of the patient.

Acknowledgements

The Working Party wishes to record its thanks to many professionals and other individuals who have assisted its work. It is particularly grateful to those individuals and organisations who prepared submissions; they are listed below.

The Working Party has drawn on a large body of legal, medical and scientific literature. References have been given only in specific support of particular points in the text. Those professionally engaged in these subjects will have access to detailed bibliographical tools.

The Working Party wishes to record its gratitude for the assistance given by Professors A Grubb and J Harris, Dr M Kemp, Professor P Lachmann and Dr R A McCall Smith. They all read through a relatively late draft of this report. At an earlier stage Professor J Underwood offered some important observations on the practice of pathology.

Submissions received

Dr Hadwen Trust for Humane Research
ICI Pharmaceuticals, Drug Kinetic Safety Evaluation Dept
Imperial Cancer Research Fund, Division of Pathology
Lord and Lady Kennet
Medical Defence Union
Medical Research Council