Chapter 5

Scientific matters : Uses of human tissue

Introduction

5.1 Once removed, human tissue may serve many beneficial purposes: in the diagnosis and medical management of individuals and in medical research, teaching, training, review and scholarship. These latter activities contribute to the public health and the public good. For example, research using human tissue may yield products which then become widely available for diagnosis or therapy. Appendix 4 lists examples of such products which are either being developed or are licensed for clinical use in the UK.

5.2 In this chapter we look at the following uses of human tissue:

- Blood transfusion
- Bone marrow transplantation
- Organ transplantation and reconstructive surgery
- Tissue replacement
- Studies of human tissue
- Diagnosis using cells
- The use of cell lines
- Pathological examination, archiving and storage
- Non-therapeutic applications

Blood transfusion

5.3 The transfusion of blood is the longest established and most familiar of the life saving therapeutic uses of human tissue. Whole blood from compatible donors, and blood components, are used routinely for the benefit of others. Whole blood may be used to replace that lost through haemorrhage and its use makes cardiac or vascular operations (bypass surgery) possible.

5.4 Blood contains red cells, white cells and platelets that circulate in the fluid plasma. Plasma is a rich mixture of nutrients and many different proteins including protective antibodies and factors that promote or inhibit blood clotting. In modern medicine, component therapy using cells or substances separated from whole blood is widely used. Fresh red blood cells can be combined with fresh frozen plasma and used to replace lost blood. Separated platelet concentrates are used to treat specific disorders, such as some leukaemias. Plasma is the starting point for a number of therapeutic products. Blood clotting factors, such as Factor VIII, are used in the treatment of haemophilia. Albumin is used to treat burns patients. Protective antibodies are used to prevent infectious disease such as tetanus or hepatitis in individuals at high risk and in the management of immune disorders.

5.5 Treatment with recombinant human erythropoietin, a genetically engineered substance that stimulates the bone marrow to produce red blood cells, has replaced the use of transfused blood in many who have anaemia caused by chronic renal failure. Artificial blood is in the early stages of clinical evaluation with the development of cell free haemoglobin. Haemoglobin, the substance contained in red blood cells that carries oxygen around the body, is either prepared from outdated human donor blood or produced by genetic engineering. The advantage of cell free haemoglobin is that it will not require cross matching with the recipient before transfusion. Current research is focused on preventing the rapid break down of the haemoglobin once it is in the body.

Bone marrow transplantation

5.6 Bone marrow transplantation is used to treat leukaemias and specific inherited diseases. It is familiar to all from newspaper accounts and appeals for donors. Donors must be carefully matched to recipients according to the genetic constitution of their cell types. The practice of culturing and transplanting stem cells, the precursor cells of the blood, is being developed. If successful, this will minimise the need for complete marrow donation.

Organ transplantation and reconstructive surgery

5.7 Organ and tissue transplantation are now well established in modern surgery. Tissue from a deceased or living donor is used for replacement or repair in the recipient. Tissue may also be transplanted from one site to another in the same patient during grafting or reconstructive surgery of damaged organs.

5.8 Tissue loss or end stage organ failure affects millions of people worldwide. In the UK alone, about 5,000 organ and corneal transplant operations are carried out annually.[1] The body part used during surgical replacement may be a complete organ (for example kidney), groups of organs (for example heart/lung), or portions of organs (for example sections of liver). Large sheets of tissue (for example portions of bone) or small pieces of tissue (for example bone chips) may be used in surgical repair. Appendix 3 offers a more complete list of the types of tissue and organs used

[1] Figures from the United Kingdom Transplant Support Service Authority

in organ transplantation and reconstructive surgery. All these procedures rely on donors; demand has long outstripped supply and waiting lists continue to rise. At the end of 1993, about 4,800 patients were waiting for kidney transplants in the UK.[1] We share the general concern at the unmet need for donor transplants, especially kidney transplants. We therefore welcome the Government's recent initiative in establishing the NHS Organ Donor Register (paragraph 4.7), but note that further measures may be required (paragraph 2.8). In the next section we discuss advances in the development of tissue substitutes that may alleviate the shortage of organs and tissue for transplantation.

Tissue replacement

5.9 Tissue engineering is an advancing science that unites the principles of biology and engineering in the development of tissue substitutes that restore, maintain or improve anatomical or physiological function. Research investigators have already attempted to develop substitutes for almost every mammalian tissue. Many of the components used in tissue engineering are of human origin, although some are artificial. Appendix 5, while not exhaustive, lists some of these developments.

5.10 Strategies for tissue replacement as an alternative to tissue transplantation include the use of:

- tissue inducing substances, such as human growth factors, to stimulate the growth of replacement cells or tissue. An example is the use of erythropoietin to stimulate the production of red blood cells as an alternative to blood transfusion (paragraph 5.5).

- isolated cells or cell substitutes. Fetal nerve cells, for example, may be transplanted into the brains of patients suffering from Parkinson's disease. The fetal cells release the neurotransmitter dopamine that is deficient in Parkinson's disease patients. The use of cell free haemoglobin as a substitute for blood transfusion is another example (paragraph 5.5).

- cells placed on or within artificial supporting matrices to form tissue masses or constructs which can be implanted. Techniques are being developed in which liver cells are contained within an artificial matrix. If successful, such artificial tissue could provide an alternative to liver transplants. For skin grafts, a supporting matrix alone can be used to stimulate the growth of the patient's own blood vessels and cells.

Research studies of human tissue and cells

5.11 Excised organs, tissue slices or snips and isolated cells may be kept viable for a limited time under experimental conditions and used for research purposes. The research may involve fundamental studies of tissue function: of gaseous exchange in the lung, for example, or the transport of substances across the placenta. Applied research may make use of infected or diseased tissue: studies of white blood cells infected with the HIV virus, or of blood vessels affected by atherosclerosis are examples.

5.12 Human tissue is used in the discovery and the development of medicines. Much of this research is performed by pharmaceutical companies. Isolated tissue may be exposed to potential medicines intended to exert a specific effect and the response of the tissue measured. The liver has an important function in breaking down drugs and toxic substances and eliminating them from the body. So studies of sections of human liver, or of isolated liver cells, are important for determining the fate of a new medicine in the liver, its toxicity and how fast it is eliminated from the body, before the medicine is tried on healthy volunteers.

Diagnosis using cells

5.13 Cells of the blood, bone marrow, amniotic fluid and chorionic villi may be cultured for analysis of the chromosomes or DNA for diagnosis of disorders such as Down's syndrome, cystic fibrosis and leukaemia.

The use of cell lines

5.14 Unmodified human cells survive under artificial conditions for only a few generations. If modified by chemical treatment or incorporation of tumorigenic viruses, cells can be made to grow continuously as 'immortal' cell lines. Some cell lines of human origin originated many years ago from the cells of malignant tumours. Some cell lines are commercially available, others are prepared by individual laboratories for specific purposes. One advantage of cell lines is that they can be used to produce large numbers of cells, and their various components. This reduces the need to collect quantities of fresh tissue. Examples of the increasing use of human cell lines for the production of therapeutic products and in medical research include:

- fundamental studies of cell behaviour and function. An example is the use of cell lines for researching the mechanisms by which cells repair the DNA damage caused by radiation;

- applied research to develop new therapeutic agents such as antiviral or anticancer medicines and to study their effects and their possible interactions with other medicines. An important element of such research is the toxicity testing of new medicines. This is one situation where the use of human cell lines may be more appropriate than the use of animals. The human lymphocyte assay, for example, is used in measuring the mutagenic potential of new medicines;

- the production of therapeutically active substances on exposure to toxins or infectious agents. These substances can be collected and manufactured as medicines. For example, the interferons produced by cells when they are exposed to viruses can be used to treat leukaemia or hepatitis;

- the propagation of human viruses that are then used to make vaccines. The production of rubella vaccine from human fetal cell lines is an example.

Studying subcellular components

5.15 Human tissue and cells can be used to isolate subcellular components for medical or biological research. Microsomes, for example, are small subcellular structures that, when isolated from liver cells, can be used to investigate the breakdown of new medicines. Perhaps the most important subcellular component, however, is the genetic material of cells, which is being used increasingly for research.

5.16 The isolation of genes coding for specific proteins has proved a powerful method for investigating the basic mechanisms underlying different biological processes, whether normal or diseased. Isolation and study of the cystic fibrosis gene, for example, indicated that it codes for a protein required for the transport of chloride ions across cell membranes. The absence of this transport in the lungs of cystic fibrosis patients accounts for the accumulation of sticky mucus in the lungs. Current research is working towards treating inherited disorders of this kind by somatic cell gene therapy which involves delivering corrective DNA to the affected tissue.

5.17 The insertion of foreign genes, which may be of human origin, into animals produces so-called transgenic animals. Transgenic animals can provide models for the study of some human diseases. Transgenic mouse strains which develop cystic fibrosis, for example, are used to test the use of gene therapy as a potential new treatment for the disease. Transgenic animals producing human proteins may eventually form a source of animal organs and tissue for transplantation or reconstructive surgery which are less susceptible to rejection than tissue from unmodified animals.

5.18 Human genes may be isolated and incorporated into microbial cells such as bacteria or yeast which are then grown in large scale biotechnology facilities to produce important medicines such as insulin, growth hormone, and erythropoietin.

Pathological examination, archiving and storage

5.19 The importance of this range of uses of human tissue is difficult to over estimate in modern biomedical practice. Almost all human tissue removed during surgical intervention or taken at autopsy is examined diagnostically by a pathologist.

5.20 The tissue, which may be fresh or fixed, is first examined macroscopically. Then representative blocks are taken, embedded in wax, cut into thin sections, mounted on glass slides, stained and examined using the microscope. The primary purpose of this histopathological examination is to establish or to confirm the diagnosis. In the case of malignant disease, the degree of spread can be ascertained. Progress, either of disease or its treatment, can be measured in certain conditions by examination and comparison of serial biopsy specimens.

5.21 These stained microscope slides and the blocks from which they were made, together with stained slides from cytological examinations (for example, for cervical cytology) must be stored so that they are available for re-examination or review as part of good practice in histopathology laboratories. Some stained blood or bone marrow films for haematological examination are also stored in this way, as are some slides made in the course of cytogenetic diagnosis. The collection, with its attendant documentation, forms the pathological archive and is a cardinal resource, not only in diagnosis and management of individual patients, but in undergraduate and postgraduate teaching and education, research, review and scholarship. Pathological archives are large; a hospital dealing with 10,000 specimens of tissue a year will generate around 25,000 blocks and some 40,000 slides. The University Department of Morbid Anatomy at the Royal London Hospital has around 4,500,000 slides, 1,500,000 blocks and 10,000 wet specimens in store.

5.22 By study of the archive, pathologists can arrive at conclusions about the natural history of a disease by obtaining a view of how it behaves in many individuals. Such study of pathological archives confirmed the link between exposure to asbestos and lung disease. By this method new varieties of tumours within a particular classification have been identified behaving either less or more aggressively. This information will, in turn, inform therapeutic choice when a new patient presents; it may minimise the extent of surgery if experience has shown that radical procedures are unnecessary or ineffective, or it may indicate the need for more radical intervention if the prognosis has proved poor with conservative therapy in the past. This approach also allows the evaluation of the effectiveness of different medicines used to treat diseases. Molecular biological methods applied to material stored many decades previously may provide genetic information and historical evidence of early occurrence of particular viral infections (Fig 5.1).

Fig 5.1

> In 1959, a 25-year old man died of unexplained causes in Manchester Royal Infirmary. The unusual symptoms included weight loss, fever, night sweats, ulcers and infections. After the autopsy, tissue samples were routinely stored and the case was reported in The Lancet. Many years later, when AIDS had been defined, the doctors who had seen the case realised that the patient's symptoms had been consistent with HIV infection. In 1987, modern PCR technology was used to test the tissue samples stored in the archive revealing that the patient's cells had indeed been infected with HIV.
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> This use of archived tissue resulted in the earliest documented case of HIV infection in Britain. The HIV strain from the late 1950s was compared with strains prevalent today and with related chimpanzee viruses. This comparison suggested that the human form of the HIV virus arose about 100 years ago when it diverged from the chimpanzee virus. This argues against theories that the HIV virus arose as the result of activities by research scientists using new techniques of genetic manipulation, for instance, during the development of polio vaccines in the Congo in 1957.
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> (Source: **Independent on Sunday** 6 November 1994)

5.23 The archive is essential in quality control and assurance. The slides are a permanent record that can be checked by independent experts in the interests of peer audit review and quality assurance. The archive may be reviewed when individual diagnoses are queried, as has proved necessary, for example, in the difficult area of cervical screening of women. Large sections of the pathological archive are occasionally reviewed where mistakes are thought to have occurred. In the United Kingdom, for instance, reviews of diseased bone samples have recently been performed.

5.24 Thus, collectively and for individual patients, careful record keeping relevant to the histopathological archive allows definition of the natural history of disease, permits identification of new disease entities, establishes the efficacy, or sometimes, the failure of treatment and permits reassessment of management if unexpected features are encountered.

5.25 In all pathological archives the material is stored anonymously, being identified by laboratory number. Thus, if the material is to be used for research purposes anonymity is readily assured, but patient identity can be established by the pathologist from the confidential diagnostic records, if the research reveals information of relevance to the treatment of the patient.

Non-therapeutic applications

5.26 The human tissues or products described so far have been used for diagnosis or therapy, for medical training and review or for research leading to therapy or adding to scientific knowledge. Use is also made of human tissue for forensic purposes, that is, connected with the detection of crime. Post-mortem examination may be performed in order to establish the cause of sudden, unnatural or violent death. The taking of blood samples for matching purposes has been practised for 50 years. To a large extent such activities are regulated by statute. The Coroners Act 1988 regulates the removal and use of tissue from the dead (paragraph 7.11.4). The Police and Criminal Evidence Act 1984, subject to changes under the Criminal Justice and Public Order Act 1994, regulates removal and use of tissue from the living. Recently, the ability to characterise DNA samples from individuals has led to the use of DNA fingerprinting in forensic science and for other purposes, such as paternity suits. The vigorous debate about the validity of using DNA fingerprinting for such purposes, its reliability, and the confidentiality that should be afforded to genetic information, is outside the scope of this report.[2]

5.27 A few legal cases have arisen because human tissue has been used for non-therapeutic purposes. In Chapter 8, we discuss a case involving the display of freeze-dried aborted fetuses as earrings (paragraph 8.3). We have made enquiries to discover whether human tissue is used in the UK in the manufacture of any non-therapeutic product, but have found no instance of such use. We know that human placenta has been used in the manufacture of face creams imported from overseas and sold in the UK, although this use has decreased substantially and is expected to cease. As we discussed in Chapter 3, the human placenta is generally treated as clinical waste (paragraph 3.8).

[2] But see the report of the US National Research Council Committee on DNA Technology in Forensic Science (1992) **DNA Technology in Forensic Science** National Academy of Sciences.