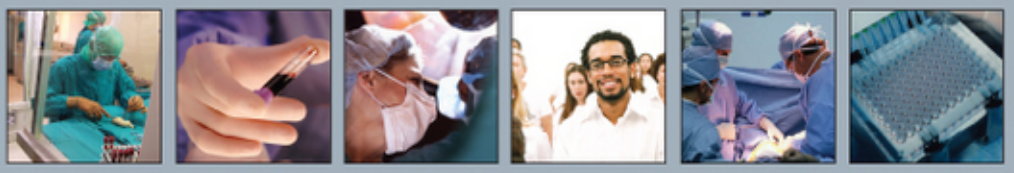

Tissue and Cell Clinical Use

AN ESSENTIAL GUIDE

EDITED BY
Ruth M. Warwick and Scott A. Brubaker

WILEY-BLACKWELL

Tissue and Cell
Clinical Use

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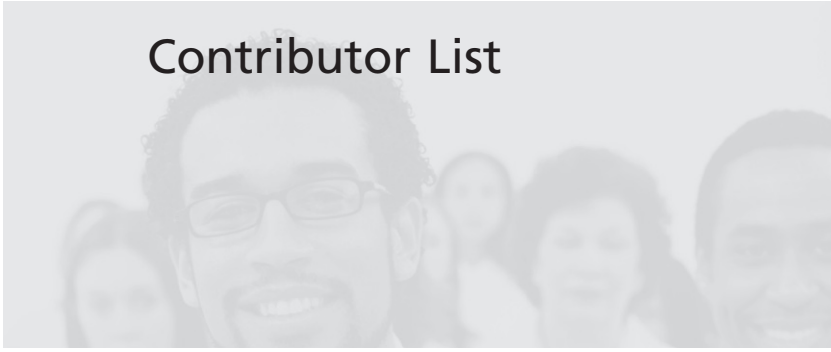

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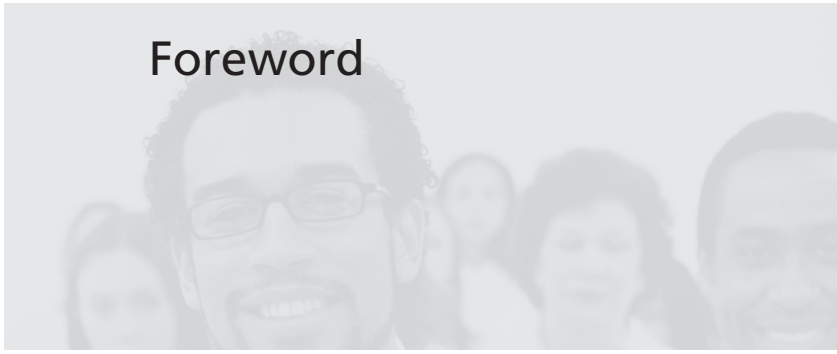
Foreword



Clinical allograft transplantation of various body parts has a long and sometimes disturbing history. Many authors have commented on the old historical events surrounding Saints Cosmas and Damian, who were from the Turkish region and practiced medicine. It was said that they were beheaded by the Emperor Diocletian in the third century AD because they were Catholics. However, they returned in the fifth century to perform the "Miracle of Black Leg" as a remarkable treatment for the soon-to-become Roman Emperor, Justinian, for a cancer of his extremity. The origin of the black limb that they transplanted was from a Moor who had died that morning, and the transplant was performed after amputation of Justinian's limb. The success of the procedure was certainly questionable but several events occurred as a result. First, almost every artist of the Renaissance became intrigued by the procedure, which resulted in hundreds of remarkable artworks displaying it. Secondly Cosmas and Damian were canonized in 570 and became saints. Finally, the alleged site of the operative procedure was in a church in the Roman Forum, which is now titled the Basilica Cosma e Damiano. Thus, the concept of transplantation from one individual to another has caught the imagination of generations during the past 14 centuries. Slowly, evidence has accrued about its benefits but, along with much success, we are now venturing into gathering information to manage and prevent adverse outcomes. Understanding biology continues to evolve.

The first clinical bone allograft transplantation was in 1881, when William MacEwen used the technique to treat a 3-year-old child with osteomyelitis of the humerus. Eric Lexer in 1908 reported four such procedures about the knee and in 1925 described a reasonable success rate with 34 joints. Since then numerous programs have reported many allograft transplants, including those of Volkov in Russia, Frank Parrish in Houston, Texas, Carlos

Ottolenghi in Buenos Aires, Istituto Rizzoli in Bologna, the Mayo Clinic and Bill Tomford, Henry Mankin, and Francis Hornicek at the Massachusetts General Hospital. Development of the National Naval Tissue Bank in 1991 by George Hyatt and Kenneth Sell was of considerable value, and its remarkable capacity to train numerous individuals led to the development of tissue banks in a variety of centers. It was Curtiss and his group who demonstrated that freezing the tissue improved outcome, and Friedlaender and Strong showed that patients with MHC class II antigens did better than those with class I or those with mismatch. There were additional benefits to improved survival of the cartilage of joint allografts from the use of glycerol and dimethylsulfoxide. Careful clinical follow-up with outcome reporting and collation provide evidence for advancement in this important, developing field. My personal interest has been in orthopedics but it is clearly only one of a variety of disciplines that have benefited from allograft use. This volume seeks to describe the clinical use of many different cell and tissue allografts to address multiple conditions.

It should be apparent to the readers of this volume that the difficulties associated with variation in cellular elements, tissue structure, bacterial contamination, and very slow regeneration result in complications and in some cases, significant system failures. It is not just the bone and other tissue allografts that have the remote but discrete possibility of developing this array of problems: all forms of allograft transplantation, including organ transplantation and haemopoietic stem cell transplants, can develop serious complications and result not only in failure of the system but potentially threaten the life of the graft recipient. Other recipients, who might receive an allograft from the same donor or the same batch of materials, can also be at risk. It is noteworthy that this book contains descriptions of recent advances in vigilance and surveillance of substances of human origin and I commend this.

The information provided by the authors in this volume clearly defines the clinical advantages and the potential and real problems associated with allograft transplant of all sorts, including those in new and developing fields such as complex tissue grafts of the hand and face as well as in my own area of large bone segments. The chapters offer the readers a major opportunity to review the advantages and as well as problems that have resulted. Ultimately, it is the balance between the advantages and the disadvantages that lead to patient benefit in the long term. This will improve the success of allografting, whether it is a stem cell or large allograft.

As a performer and caring physician for many patients with allograft bone transplants and as a teacher, it is my privilege and my honor to have the opportunity to introduce the subject with this foreword. I am hopeful that some of this discussion will increase the depth of understanding of the excellent presentations by the multiple outstanding authors of the chapters, and that this important didactic book, with its case studies and learning points

in each chapter, will continue the critically important task of teaching and educating professionals working in, and regulating, diverse fields associated with tissue and cell allografting.

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Preface

This book on the use of donated tissues and cells is the third in a series of three. The first was published in 2009. Its 13 chapters focused on the human dimensions of donation, addressing the topic from the history of the discipline, through donor recruitment and consent, medical and behavioral history taking, to the role of donor testing and the management of test results. Case studies demonstrated the diversity of the field in different cultural and economic realities, and issues relating to the care of the professionals who undertake rewarding but sometimes arduous, emotional duties were discussed. The first book also covered aspects relating to the donation of hemopoietic stem cells, the reproductive context, and the role of clinical governance in tissue and stem cell banks.

The second book is published in parallel with this third book and covers all aspects of recovery and processing of tissues and cells, including collection of reproductive donations and hemopoietic stem cells, and the training of staff in these disciplines. The foreword to the first book was written by Professor Rafael Matesanz from the Spanish National Transplant Organisation in Madrid. Dr Matesanz describes two things that should always be strictly linked to assure a solid foundation for a transplant system to offer the best opportunities and results for patients: technical quality standards and ethics. This is true for the donation aspects and for the use of donated tissues and cells. We invited international experts to collaborate with us in developing this book so that our readers would have access to a broad reference from the expert surgeons and physicians using tissues and cells, with evidence from the literature on the clinical benefits of these invaluable donations.

This volume is designed in a similar format to its sister books. It has 20 chapters and includes cases and learning points. We cover the same fields as the first two books and deal with the application of tissues and cells by those working in the clinical field. Similarly, this volume has a

cross-continental editorship and chapters co-authored by experts in their field with representation from all over the world in an attempt to provide a global perspective. We are especially honored that Dr Henry Mankin has written the foreword to this third book. He has commented on the long history of the use of allografts and the advances that have made their use an essential part of the armamentarium of doctors in many specialties. This is an important point from him because he has been recognized as an innovator and expert clinician in the use of allografts in orthopedics, in which he has been working for over 50 years. He started orthopedic residency at the Hospital for Joint Diseases in New York City and later became orthopedist-in-chief at Massachusetts General Hospital and a professor at Harvard. He has several specialty interests including in Gaucher's disease and in the use of major bone allografts. He has developed a computerized system for following the 18 000 tumor cases that he and his unit have treated over many years. The more than 600 papers published by his team is an extraordinary literature on the evidence of benefit from the use of donated bone. He has recognized in his foreword that although allografts carry many advantages, there are also risks associated with their use. We have structured this book in a way that allows clinicians to weigh up these two opposing aspects of allografts and to make informed choices on when to use them. Information is provided on how to recognize adverse reactions and to collaborate with the clinical allograft network to promote maximum safety.

The book starts with a chapter on the ethics of the use of allografts, a subject fundamental to the continuing support of the donating public. We follow with chapters on clinical governance in hospitals, dental surgeries, and other establishments that use allografts. In Chapter 3 existing vigilance and surveillance schemes for tissues and cells from around the world are described. Vigilance activity is generally so recent in this field that most of the references that have been provided are web based. This reflects an important new development in the field that will undoubtedly increase safety of allografts, which is especially important in the context of global distribution. Chapter 4 reviews transmission of disease by organs, tissues, and cells. This is followed in Chapters 5–20 with specific descriptions of the use of allografts in surgical specialties such as vascular, cardiac, and orthopedic surgery, as well as neurosurgery, sports medicine, dentistry, burns, and the use of skin substitutes for a variety of other applications. There is a chapter on ophthalmic use of tissues and cells, and in the innovative areas of complex composite vascular tissue grafting such as hand and face transplantation, which has received huge lay press interest. A specific chapter describes the rapidly evolving work in the use of hemopoietic stem cells and mesenchymal stem cells. Our authors also relate areas of recent developments in the use of stem cells, with a chapter covering embryonic or neural stem cells and the central nervous system with a particular focus on Parkinson's disease, multiple sclerosis, spinal cord damage, and stroke. To round

out this exciting innovative approach to therapy, there is a chapter on pancreatic islet cells and another on cardiac stem cells. We are most grateful to Dr Stephen Minger for reviewing the stem cell chapters. We finish with a chapter on the use of donated gametes in the assisted reproduction sector.

We hope that this set of three sister books provides a comprehensive overview from experts in their fields, of all the multidisciplinary aspects of donation, recovery, and use of donated materials of human origin. Our aim is that they will help inform both professionals and regulators on recent developments in this diverse and unique field of medicine. Ultimately these books are about the generosity of donors, the skills of the professionals, and communities of individuals working together for the benefit of patients around the globe.

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1 Ethical Issues Regarding the Use of Human Tissues and Cells

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Introduction

Over the past two decades the use of human tissues and cells for transplantation has steadily increased. In the United States (USA), for example, 2,141,960 tissue grafts were distributed by American Association of Tissue Banks (AATB)-accredited tissue banks in 2007 (2007 AATB Annual Survey Results, Tissue Banks in the United States, May 2010). The AATB reported that tissue donor recoveries in the USA have continued to rise with every survey [1] (Figure 1.1).[1] Other countries, such as Spain and Slovakia, have also witnessed a rapid increase in donation of tissues. It is not clear, however, if this increase is in every case a response to need, a consequence of required death referral[2] or of other process improvements, or if tissue referral, procurement, and processing are growing as business opportunities.

The field of hematopoietic stem cell (HSC) transplantation has witnessed remarkable development from a highly experimental and risky procedure in the 1970s to a continuing complex procedure with inherent risks but is now a widely applied therapy for a variety of lethal conditions of the bone marrow [2].

---

[1]Contributing to this was the establishment of first person consent registries in many states, and most important was a change in federal law that required all deaths or imminent deaths to be referred to the local organ procurement organization or a tissue bank. These organizations approach families for consent or authorization using specially trained personnel and they provide call centers that handle all referrals.
[2]In the USA per Centers for Medicare & Medicaid Services (CMS) Final Rule – the Conditions of Participation.

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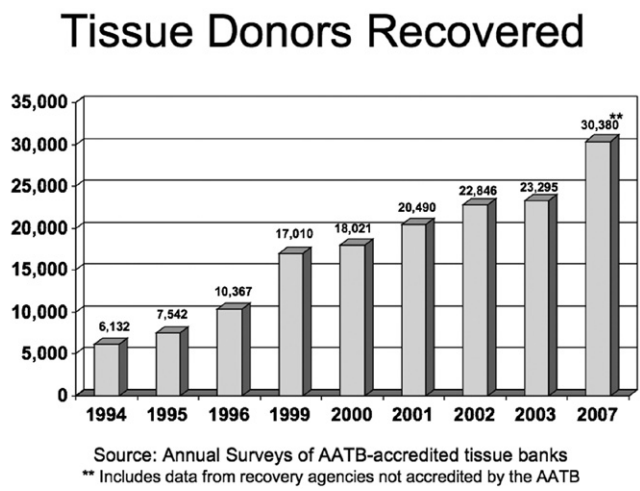

Figure 1.1 Increasing number of tissue donors in the USA [1]. (Reproduced by permission of American Association of Tissue Banks, 2007 AATB Annual Survey Results, Tissue Banks in the United States, May 2010.)

This dynamic development is in part due to scientific advances, such as in histocompatibility matching, immunosuppression, and prophylactic treatment of infections. Another reason for the rapidly expanding activities in human cells and tissues for transplantation (HCTT) is the increasing international exchange of these human donations. Collaborative efforts from more than 60 registries of unrelated volunteer bone marrow and other types of HSC donor have expanded the pool of potential donors for these patients from their immediate and extended family through to close to 14 million people globally. The success of some tissue banking systems has led to excess supply and allowed export of certain tissues to countries in need. The export of corneas retrieved in the USA, for instance, has grown from 7% (of the total number of corneas available for transplantation) in 1990 to 29% in 2000 [3]. Anecdotal reports state that 10–15% of the tissue distributed by USA tissue banks (excluding eye banks) is sent outside of the USA. The Canadian Council for Donation and Transplantation report in their surveys that more than 80% of the tissue used in Canada is imported from the USA.[3]

However, data on global use and exchange of tissues are patchy with poor levels of traceability. On the other hand, the unrelated HSC programs are quite tightly controlled by the bone marrow donor registries and cord blood banks, and both activity levels and adverse events data are reported annually

[3] Supply of Human Allograft Tissue in Canada. April 2003, CCDT. http://www.organsandtissues.ca/s/wp-content/uploads/2011/11/Supply-Allograft.pdf. Accessed April 2012.

by the World Marrow Donor Association (WMDA) (http://www.worldmarrow.org). The World Health Organization (WHO) has also accumulated data on various organ and tissue transplantation rates derived from government sources in its Global Knowledge of Transplantation (http://www.who.int/transplantation/knowledgebase/en).

The idea of transplanting tissues has a longstanding history. A frequent reference is to the legend of Saints Cosmas and Damian, who attempted to transplant a limb from a deceased moor to a white nobleman in the 3rd century AD. Van Meekeren, a Dutch surgeon, reported in 1668 the first successful bone transplant performed on a Russian soldier where a piece of canine skull was used to fill the defect in an injured soldier's skull. When this transplant was discovered he was excommunicated because the treatment was seen as un-Christian. To return to the good graces of the Church, the soldier asked for the bone to be removed but the graft had already incorporated and healed [4]. Centuries later the surgeon Alexis Carrel expressed his view of the need for organ and tissue transplantation when he stated, "if it were possible immediately after death . . . to transplant the tissues and organs . . . no elemental death would occur, and all the . . . parts of the body would continue to live. A supply of tissues . . . would be constantly ready for use . . . and could be sent to surgeons who need them" [5].

From these early times, tissue banking organizations have now grown to many hundreds of establishments providing millions of tissue grafts for transplantation annually, often with excellent success. The early Bone Marrow Registries have grown to more than 70 organizations, and perhaps 200 cord blood banks exist globally. But even if medical advances have allowed cell and tissue transplantations to become standard procedures that are readily accepted by many patients across nations, cultures, and religions, new scientific and ethical challenges have emerged.

One of these challenges is the development of a solid evidence base for clinical and policy decisions regarding HCTT. What is the need and demand for each tissue in each country every year? Can communities be self-sufficient from the tissue donations from their own population? When are cell or tissue transplants the best treatment option, and when is a product being used just as a convenient solution? For example, when is a human heart valve better or worse than a mechanical or a porcine valve? How can governments ensure that precious and rare tissues and cells be optimally used? These issues gain particular importance once donated substances of human origin are highly processed and start to be considered as tradable goods like any other.

The challenge of maintaining both confidentiality and transparency is a responsibility that exists through every step in donation, banking, allocation, and transplantation of human cells and tissues. There has been a longstanding effort in organ transplantation to establish and promote transparency about the availability and allocation of human organs. In tissue

transplantation, some health authorities are uncertain of the number of tissue establishments operating in their country, let alone the number of donated, transplanted, exported or imported tissue [6]. Transparency, however, is a key requirement for public trust. This trust is regularly challenged, for example, when bodies or component tissues are reported by the media to have been sold by Funeral Home Directors or when a young patient dies after a dubious experimental stem cell treatment. A clear and well-implemented framework of ethical principles may help avoid such scandals. Detailing how respect for autonomy, stewardship, and fair access to treatment by these special donations is going to be achieved and maintained, together with applying appropriate quality and safety standards, is an important basis for the future development of HCTT.

This chapter outlines major ethical principles and issues of HCTT. It does not enter into issues arising from tissue or cell donation as these have been treated extensively elsewhere [7]. Cell and tissue transplantation are considered separately, as they are in fact two rather distinct fields, while the use of germ line tissues and cells are covered in Chapter 20. The complexity of issues that will need consideration if and when the decision is made to use human embryonic stem cells and induced pluripotent stem cells (IPS) cells has yet to be defined as the science turns slowly from fiction to fact.

A normative framework for HCTT

There are several general ethical rules and principles that cut across the various fields of cell and tissue transplantation and, indeed, organ transplantation. The principle of respect for autonomy requires that any donation be based on informed, voluntary consent. In the case of a deceased donor who in life has not opted out from donation, this may suffice as authorization, but even in presumed consent systems the donor's family is usually asked for approval, acknowledging the psychological implications a donation may have for them. Also their cooperation is desired for providing a medical and behavioral history.

The concept of stewardship is also inspired by respect for autonomy of the donor: it wishes to honor the intention of the donor – to help another suffering person with his or her gift, a part of one's own body. Charging unjustifiable fees for processing the cells or tissues or otherwise turning the gift into a commodity just like any other would be incompatible with the idea of serving as the steward of a human tissue or cell gift that one was entrusted with.

Stewardship also requires making optimal use of the donated material. Using the donation in the most efficacious way can also be argued for within the principle of beneficence. Quality and safety requirements, on the other hand, follow from the ethical principle of non-maleficence: risks to the (live) donor, the recipient and third parties are to be minimized. The principle of

Box 1.1 Elements of a normative framework for HCTT

An international consensus has emerged on the following ethically relevant rules and concepts

Transparency (while protecting privacy of donor and recipient)
Evidence-based standards for procurement, processing and clinical use
Quality, safety, and efficacy
Informed and voluntary consent for donation as well as for receiving a transplant
Stewardship and non-commercialization
Equitable access and fair allocation

Underlying general ethical principles

Respect for autonomy – beneficence – non-maleficence – justice

non-maleficence could also be used to argue against paying donors or their families, as this may encourage dishonesty about the medical history, with the consequence of possible harm to the donor during the donation and to the recipient from an unsuitable product.

Paying for donation could also be considered as being in conflict with the principle of justice. More donors or families with low socio-economic status would respond to financial incentives for donation, whereas high prices for the respective cell and tissue products would favor transplantation of affluent individuals and patients from high resource countries. If human cells and tissue are to be considered not as a commodity but as a community resource their distribution becomes a justice concern, requiring criteria and processes for defining equitable access and fair allocation.

International guidance documents – such as the World Medical Association Statement on Human Organ Donation and Transplantation [8], the Council of Europe's Additional Protocol to the Convention on Human Rights and Biomedicine [9], the European Directive 2004/23/EC [10] and the WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation (2010) [11] – concur on these fundamental principles and rules (Box 1.1).

Ethical issues of HCTT

Once a normative framework of HCTT has been defined, the practical challenge lies in specifying the meaning of these overarching principles and rules in the light of ethical issues that arise in the different stages of donation and transplantation activities – from procurement to processing, testing, storage, allocation and distribution.

Table 1.1 Central ethical issues in the regulation of human cell (HC) and human tissue (HT) transplantation. (Reproduced with permission from Schulz-Baldes A, Biller-Andorno N, Capron AM (2007) International perspectives on the ethics and regulation of human cell and tissue transplantation. Bulletin of the World Health Organization 85, 941–948.)

Issue	Agreement	Disagreement
Consent for HC/HT removal	• No HC/HT removal without consent • Informed consent for donation from living donors • Disclosure of possible limitations to withdrawing consent	• Informed versus presumed consent in deceased donation? • Role of the next of kin ("family veto") in deceased donation? ○ Obligation to inform about possible profit-making, international circulation or cosmetic applications?
Confidentiality of donor data	• Confidentiality of donor data (with exceptions)	
Unpaid HC/HT donation	• Unpaid donation • Removal of financial disincentives for donation ○ Only not-for-profit institutions in donation discussions and the promotion of donation	
Fair HC/HT procurement	• Fair criteria for donor identification and selection	○ Binding priority of organ over HC/HT recovery?
Stewardship for donated HC/HT	• Obligation to honour and realize donor intent • Option to veto HC/HT use for research or education • No discriminatory restrictions of HC/HT use ○ Stewardship, effectiveness, accountability, fair pricing, responsiveness to local and/or national needs and fair allocation are more important than institutional for-profit/not-for-profit structure	○ Option to veto HC/HT use abroad or for cosmetic applications?
Quality and safety management	• Necessity of quality and safety management • Long-term follow-up of donors and recipients	• Balance between quality, safety and HC/HT availability in resource-poor settings?

Table 1.1 (*Continued*)

Issue	Agreement	Disagreement
Fair distribution of processed HC/HT	• Need for allocation criteria and prioritization rules despite limited scarcity ○ General priority of HC/HT use for life-saving over life-enhancing and cosmetic purposes ○ General priority of local and/or national self-sufficiency	○ Scope of allocation criteria and prioritization rules: institutional, national, subregional? ○ Institutional reciprocity as an allocation criterion? ○ For-profit organizations in HC/HT distribution? ○ General priority of subregional self-sufficiency? ○ International HC/HT circulation to subsidize public health care?
Consent for HC/HT transplantation	• No HC/HT transplantation without voluntary and informed consent	○ Obligation to inform recipients about profit-making and international circulation? ○ Limits of consent for medically contested uses?

• normative agreement or disagreement was analogous to that for organ transplantation;
○ normative agreement or disagreement was specific for HC/HT transplantation.

Whereas some ethical issues are highly specific to a certain kind of intervention or graft, there are also several cross-cutting themes. Table 1.1 shows issues that emerged at the 2006 International Symposium on Ethical and Policy Issues of Human Cell and Tissue Transplantation that was organized by the University of Zurich in collaboration with WHO, outlining areas of agreement and disagreement among meeting participants.

The question of financial incentives, although related to the donation, will be considered, as it relates to the larger context of commercialization of cell and tissue transplantation. The focus, however, will be on selected issues regarding processing, access and allocation and recipient consent in HCTT, respectively.

Ethical issues: tissue transplantation

Tissue transplantation comprises a heterogeneous group of grafts and procedures, including the transplantation of vessels, heart valves, bone allografts, tendons, skin, corneas, and complex tissues, such as hands and face. These grafts are used in a variety of disciplines, for example: orthopedics and sports medicine, neurosurgery, ophthalmology, craniofacial, urology, cardiothoracic, vascular, dentistry, and plastic surgery.

From an ethical point of view, there are several possible ways to categorize different allografts (Box 1.2). One relates to the degree of processing applied to the donation. There seem to be morally relevant differences between

Box 1.2 Ethically relevant criteria for distinguishing tissue transplants

Tissue transplants may be distinguished according to the following ethically relevant criteria

Degree of processing
Link to individual donor as source of transplant
Temporary versus permanent transplants
Medical purpose (life saving versus enhancing)
Therapeutic alternatives
Established versus experimental therapy
Preservation methods and storage conditions
Need for immunosuppression (hand and face transplantation)
Availability of the type of tissue and size matching criteria
Living donor versus deceased donor

allografts such as an entire bone versus a screw that contains a small amount of bone powder: whereas we would think of the bone segment primarily as a part of an individual donor's body we might be more inclined to consider the screw as a commercial, although somewhat special, product.

Another psychologically relevant distinction relates to how obviously the donor is the source of the graft. This particular issue is relevant in composite grafts; receiving a recognizable hand or face may trigger more far-reaching questions about the relationship between body and identity. Similarly, the questions of permanence of the graft, whether it is transient or permanent will affect the degree to which the recipient will need to confront the task of integrating the graft into his or her own body and sense of self.

Some transplanted tissues have an important impact on quality of life or even survival (such as skin allografts for burn victims), whereas others may achieve only moderate improvements or aim at enhancing an already fair quality of life (such as a knee replacement for arthritis). Some tissue transplantations, such as autologous bone, are the clear gold standard for a certain indication, whereas in other cases comparable or even superior therapeutic alternatives may exist. Some transplants (for example, human embryonic stem cells) remain highly experimental, whereas others, such as cryopreserved heart valves, have been used successfully for decades.

Tissue grafts differ in the way they are preserved and the subsequent environmental storage conditions which they need. This can affect concepts for allocation as these will need to be quite different if a tissue can only be stored short-term vis-à-vis a graft that can be stored for a long period. For instance, tissues with a short preservation time need to be used quickly and cannot be transported over long distances. Another important factor affecting access to therapy using transplantation relates to the need for