Tissue and Cell Processing

AN ESSENTIAL GUIDE

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Foreword

It gives me great pleasure to introduce this book, which covers the historical context of tissue and cell processing since the first allograft implantation was introduced clinically to current practice in tissue and cell banking. Its publication is timely – in the golden jubilee year of the first heart valve allograft (homograft) operation in 1962. Even then, it was clear that allografts had significant benefits over mechanical valves, which continue to require lifelong anticoagulation and carry the increased risk of stroke or bleeding, a particular problem in populations with limited medical staff and facilities. Our only disappointment was that it became apparent that the homograft did deteriorate over a number of years and would eventually need replacement. This led me, in 1967, to perform the pulmonary autograft, where the patient's pulmonary valve is transplanted to the aortic position and the pulmonary valve is replaced with a pulmonary allograft, where it is subjected to much lower pressures and therefore should have improved longevity. This continues to be *Work in Progress*. Research in tissue engineering and stem cells currently holds great promise for donated cardiac tissue.

From those early pioneering days we have seen the development of highly professional, uniform systems, embracing all aspects of organ and tissue transplantation, enshrined by the guiding principles issued by the World Health Organization.

This book describes parallel developments in other clinical specialties where tissues or cells have been donated for the benefit of others. It is not surprising that many common themes emerge across these specialties. It is a comprehensive guide to the level of technical complexity

and precision required, where surgeons can be assured that the graft they receive for implantation will meet a particular specification. I have no doubt this publication will be regarded as a required handbook for tissue banks throughout the world.

Donald Ross

Preface

It was the development of techniques to preserve donated tissues and cells that gave life to the field of tissue and cell banking. This ability to store is what makes tissue banking different from organ transplantation. The banking activities of washing, cutting, shaping, cell separating, decontaminating, preserving, packaging, storing and distributing have become almost industrial in many countries, with large numbers of “products” being prepared and distributed internationally. But these are not like other healthcare products. Their human origin gives them a very particular nature, associated with the fact that they have been donated by people who want to help others and with the inescapable knowledge that they carry some risk for recipients, usually very small but sometimes unpredictable or undetectable. On the spectrum of healthcare substance processing, tissues and cells sit with blood components, somewhere between organ transplantation at one extreme and medicines manufacture at the other. This second book in a series of three explores those aspects of tissue and cell processing that aim to preserve and respect the special, emotional aspects tied to their human origin, while maximizing safety and quality through the application of quality standards and approaches similarly applied in other fields, such as the manufacture of aspirin or, for that matter, cars!

The development of methodologies to preserve tissues and cells brought with it a number of advantages. Once tissues could be made readily available for human application at a later date, shortages could be avoided with banked inventories providing various sizes and types as required. Better utilization of invaluable donations became

achievable by making multiple grafts from single donations: the cortical bone of a femur could be used to prepare strong weight-bearing rings for spinal surgery while the cancellous bone of the same femur could be morcelized and provided as an effective packing material to fill bony defects. With this greater donation utilization came the opportunity to cut and shape certain graft types in advance, saving time in the operating theatre. Allografts are not only transplanted, they can be infused, implanted or transferred, and prepared for specific applications. For example, the 120 mL of collected cord blood becomes 25 mL of concentrated progenitor cells, the placental membrane becomes a batch of clean 1 cm square patches for ocular surgery, and one semen donation becomes a series of aliquots of washed spermatozoa. But apart from this increase in efficient use of donations, tissue and cell banking brought opportunities to increase safety by removing those parts of the tissue or cell donation that were not necessary for clinical effectiveness or by applying decontamination or sterilization methods to remove bacterial, fungal or, in some cases, viral agents.

Tissue and cell processing brings these indisputable benefits but it also brings its own risks. The literature has documented rare but sometimes tragic results of environmental contamination and cross-contamination, of the extension of donor-derived risk to multiple recipients through large scale processing, of the accidental mixing of gametes or embryos or the reliance on sterilization methods that were not properly validated or effective. The potential for making profit from tissue and cell recovery and processing exacerbates the risk that income will be prioritized over safety and quality. For all these reasons, the world of tissue and cell processing is increasingly regulated. Professionals and regulators alike call on the field to maximize the benefits of processing and storage, while minimizing the risks, by applying the knowledge and tools of

“manufacturing,” particularly those of the pharmaceutical industry, to achieve consistently high levels of quality and safety.

In this book, in line with the other two books in the series, we have drawn on the experience and expertise of international experts to capture and describe, in a didactic way, the key principles of safe and effective banking in this “industry” that is like no other. The regulatory framework is described and chapters address the scientific principles behind tissue and cell preservation, decontamination and sterilization – the added value of tissue and cell banking processes. Many of the processes that have been applied over the years have developed in a “cottage industry” way and been copied from bank to bank; Chapter 7 describes how facilities can meet today’s regulatory expectation that processes be properly validated and thoroughly documented. The importance of risk management, traceability and coding and personnel training are all addressed by experts who have learned through experience that these aspects are crucial to providing safe allografts. Finally, a series of chapters address the specificities of particular substance processing from skin or bone marrow to gametes and embryos.

Despite huge developments in science and technology, donated human tissues and cells are frequently still the best option for replacement of damaged or diseased tissues or cells in patients or for achieving successful pregnancy. In parallel, however, novel and creative approaches are being developed as described in Chapter 18. Traditional tissue and cell banking is likely to co-exist well into the future, providing an essential clinical service, with exciting, more sophisticated new processes such as cell culture, gene therapy or tissue engineering.

The editors of this book are most grateful to all the authors who worked together, always trying to ensure that the “best

practice” picture they presented reflected varying geographical and regulatory realities. Many of the authors who worked together to write these chapters had not known each other previously but have forged strong professional relationships through this collaboration. The editors would also like to thank Mr Donald Ross for writing the Foreword. Now retired, Donald Ross was a pioneering cardiac surgeon who performed the UK’s first heart transplant in 1968, having already been the first surgeon in the world to use an aortic homograft in 1962. He went on to advance the use of pulmonary homografts and originated the pulmonary autograft operation which is now known as the Ross Procedure. The first book in this series was published in 2009 and addressed tissue and cell donation. The third is published in parallel with this book and addresses tissue and cell clinical use. The editors hope that these three books together provide a comprehensive guide to the provision of safe and effective tissues and cells for human application through ethical and safe donation procedures, validated antimicrobial and preservation processes, and appropriate clinical application.

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Regulations and Standards

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Introduction

The primary purpose of statutory regulations is to serve as a common framework for ensuring with confidence the current state of the art on the quality and safety of tissues and cells for therapeutic benefit. Equally, the regulations and linked guidance should be compatible on a wider level to encourage equitable distribution between countries, where regulations may be similar and well established, in early development, or in their infancy. Many countries have implemented or are refining their healthcare services to provide a better standard of care to patients and to enhance the use of tissues and cells for clinical applications. The steps involved in the processing of tissues and cells are critical activities and require the application of specific controls to prevent contamination and cross-contamination, as well as to maintain quality and safety. This chapter gives an overview on the status, history, and scope of key regulations; the practical aspects of implementation; the interface with advanced therapy medicinal products

(ATMPs); medical devices; biologics; and some global perspectives.

The therapeutic application of tissues or cells is preceded by a series of complex and inter-related activities, from donor selection and screening, infectious disease testing, tissue and cell recovery, processing, temporary or long-term storage, and distribution for use in the clinical setting. The organization and delivery of healthcare systems are structured and operate quite differently, according to resources and health programs, to address epidemiological characteristics of the endemic population. To encompass these diverse organizations, and their inter-linked activities, a tissue establishment can be defined as:

> a tissue bank or a unit of a hospital or another body where the activities of processing, preservation, storage or distribution of human tissues and cells are undertaken. It may also be responsible for the procurement or testing of human tissues and cells [1].

Organizations in healthcare services or the commercial sector performing one or typically more of these activities should be authorized by their national regulating body and are expected to verify compliance with appropriate requirements, so governing the quality and safety of tissues and cells.

Professionals working in the tissues and cells sector have not been wholly amenable to “allografts” being referred to as “products” or “devices;” and some have reservations regarding the use of the term “manufacturing” being applied in the context of human tissues and cells donated altruistically for the benefit of others. However, regulatory preferences and established terminology of other healthcare sectors often over-ride the human dimension in this donation-related work and such terms are commonly applied. This chapter discusses the requirements and