Transplantation of Composite Tissue Allografts

Charles W. Hewitt and W. P. Andrew Lee
Editors
Chad R. Gordon
Associate Editor

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Springer

Editors
Charles W. Hewitt, Ph.D.
Professor of Surgery
Head, Division of Surgical Research
UMDNJ-Robert Wood Johnson Medical School
Cooper University Hospital
Camden, New Jersey

W. P. Andrew Lee, M.D.
Professor of Surgery and Orthopedic Surgery
Chief, Division of Plastic Surgery
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

Associate Editor
Chad R. Gordon, D.O.
Chief Resident
Department of Surgery
UMDNJ-Robert Wood Johnson Medical School
Cooper University Hospital
Camden, New Jersey

Cover illustration: The image depicts Saints Cosmas and Damian transplanting a lower extremity composite tissue allograft in place of an elder's amputated limb (c. 286 A.D.)

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This book is dedicated to the next generation; namely, Nicole, Ryan, Noah, and Zachary, along with my former students, residents, and fellows. They represent the future in terms of yet unrealized accomplishments and discoveries that await fruition.

Charles W. Hewitt

This book is dedicated to the research fellows, surgical residents, and medical students who have worked in our laboratories at Hopkins, Mass. General, and Pittsburgh in the last two decades. Their intellect, enthusiasm, and achievements are inspirational for future generations of contributors in composite tissue allotransplantation.

W. P. Andrew Lee

I would like to dedicate this book to my dearest wife, Abbey, in gratitude for her everlasting encouragement and support. And to our precious son, Austin, who has provided endless nights of laughter and smiles.

Chad R. Gordon

Foreword: The Import of Composite Tissue Transplantation

Four decades have passed since allogeneic transplantation first became a clinical reality. Although I have been passionate throughout my career in regards to solid organ transplantation, it gives me great pleasure to observe the success in the transplantation of composite tissue allografts, such as the first successful human hand transplant. I, along with many of my colleagues, have witnessed numerous patients who had suffered life-changing injuries benefit dramatically from successful composite tissue transplantation.

In order to fully appreciate these recent accomplishments, one must realize that a "composite tissue transplant" entails a significant challenge, encompassing a unique tissue combination in each specific case. For comparison, when performing a kidney or liver transplant, the transplanted organ's function can be quantified by several physiologic and biochemical metabolic processes. In this field, however, defining post-operative allograft function, in terms of its various components, can easily become quite puzzling.

This book, *Transplantation of Composite Tissue Allografts*, is wonderfully detailed, containing a thorough overview of important related subjects in the section of Composite Tissue Transplantation. This blossoming field, driven by some of the world's most compelling physicians, scientists, and surgeons, is quite inspiring to all. And it is our hope that this book will both inform and excite all who are interested in helping those patients benefit from transplantation of composite tissue allografts.

Thomas E. Starzl

Preface

This book reviews, updates, and synthesizes the recent accomplishments and ongoing research in the field of composite tissue allotransplantation (CTA). The volume focuses on the immunology, biotechnology, and bioengineering of CTA, as these areas have demonstrated the most growth within the field in the last five years.

The text presents the entire scope of CTA in a comprehensive format. This effort details the state-of-art advances of CTA and includes the numerous accomplishments of premier scientists and physicians from around the world engaged in the field. Significant advancements in the evolution of CTA are detailed from the historic legend of "Cosmas and Damian" through the most recent controversial topics of hand and face transplantation.

Transplantation of Composite Tissue Allografts is an ideal and valuable resource for a diverse group of physicians, scientists, researchers, residents, and students. This book will both inform and excite all who are interested in helping patients benefit from transplantation of composite tissue allografts.

Charles W. Hewitt
W. P. Andrew Lee
Chad R. Gordon

Contents

Contributors

Galip Agaoglu, M.D.
Division of Plastic Surgery,
The Cleveland Clinic Foundation,
Cleveland, Ohio

Patricio Andrades, M.D.
Division of Plastic and Reconstructive
Surgery, Department of Surgery,
Jose Jaoquin Aquirre Clinical
Hospital, University of Chile
School of Medicine, Santiago,
Chile

Milton B. Armstrong, M.D.
Division of Plastic Surgery,
Department of Surgery, University
of Miami, Miami, Florida

Rachael R. Ashcraft, M.D.
University of Louisville, Division of
Plastic Surgery Research, Louisville,
Kentucky

Clement K. Asiedu, Ph.D.
Clinical Instructor of Surgery,
University of Alabama at Birmingham,
Department of Surgery, Birmingham,
Alabama

Lionel Badet, M.D., Ph.D.
Department of Transplant Surgery,
Edouard Herriot Hospital,
Université Claude Bernard Lyon,
Lyon, France

Joseph C. Banis, M.D.
Clinical Associate Professor,
University of Louisville, Division
of Plastic and Reconstructive Surgery,
Department of Surgery, Louisville,
Kentucky

John H. Barker, M.D., Ph.D.
Professor of Surgery, University
of Louisville, Director, Plastic Surgery
Research, Louisville, Kentucky

Kirby Black, Ph.D.
Department of Biotechnology,
Kennesaw State University, Kennesaw,
Georgia

Warren Breidenbach, III, M.D.
Assistant Clinical Professor of Surgery,
University of Louisville, Kleinert,
Kutz Hand Care Center, Louisville,
Kentucky

Au H. Bui, M.D.
Division of Transplantation,
Department of Surgery, David Geffen
School of Medicine at UCLA, Los
Angeles, California

Linda C. Cendales, M.D.
Hand and Microsurgery and Composite
Tissue Allotransplantation, Orthopedic
Section, NIAMS, National Institutes of
Health, Bethesda, Maryland

Zsolt T. Csapo, M.D.
Visiting Assistant Professor, University of Texas at Houston School of Medicine, Division of Immunology and Organ Transplantation, University of Texas Health Science Center at Houston, Houston, Texas

Michael R. Cunningham, Ph.D.
Professor of Psychology, University of Louisville, Department of Communications, Louisville, Kentucky

Michael Diefenbeck, M.D.
Assistant Professor of Surgery, University of Munich, Munich, Germany

Jean-Michel Dubernard, M.D., Ph.D.
Professor of Surgery, Université Claude Bernard Lyon, Department of Transplantation Surgery, Edouard Herriot Hospital, Lyon, France

Marek Durlik, M.D.
Polish Academy of Sciences, Division of Transplantology, Department of Surgical Research and Transplantology, Medical Research Center, Central Clinical Hospital, Ministry of Internal Affaires, Warsaw, Poland

Assia Eljaafari, M.D., Ph.D.
Department of Transplantation Surgery, Université Claude Bernard Lyon, Edouard Herriot Hospital, Lyon, France

Bence Forgacs, M.D., Ph.D.
Division of Immunology and Organ Transplantation, University of Texas Health Science Center, Houston, Texas

Cedric G. Francois, M.D., Ph.D.
Senior Research Associate, Department of Physiology & Biophysics, University of Louisville, Louisville, Kentucky

Allen Furr, Ph.D.
Associate Professor of Sociology, Department Chair, University of Louisville, Louisville, Kentucky

Vijay Gorantla, M.D.
Research Fellow, Division of Plastic Surgery, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Chad R. Gordon, D.O.
Chief Resident, Department of Surgery, UMDNJ-Robert Wood Johnson Medical School, Cooper University Hospital, Camden, New Jersey

Scott A. Gruber, M.D., Ph.D., M.B.A.
Professor of Surgery, Chief, Section of Transplant Surgery, Wayne State University School of Medicine, Harper University Hospital, Detroit, Michigan

Mark A. Hardy, M.D.
Professor of Surgery, Columbia University, New York, New York

Rhonda Gay Hartman, J.D., Ph.D.
Center for Bioethics and Health Law, Visiting Professor, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Charles W. Hewitt, Ph.D.
Professor of Surgery, Head, Division of Surgical Research, UMDNJ-Robert Wood Johnson Medical School, Cooper University Hospital, Camden, New Jersey

Gunther O. Hofmann, M.D., Ph.D.
Department of Surgery, Klinikum Grosshadern, Ludwig-Maximilians-University Munich, Munich, Germany

Elaine K. Horibe, M.D.
Research Fellow, Division of Plastic Surgery, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Ricardo Jimenez-Lee, M.D.
Chief Resident, Division of Plastic Surgery, University of Miami, Miller School of Medicine, Miami, Florida

Neil F. Jones, M.D.
Professor of Surgery, David Geffen School of Medicine at UCLA, Division of Plastic & Reconstructive Surgery, Department of Orthopaedic Surgery, UCLA Medical Center, Los Angeles, California

Barry D. Kahan, M.D., Ph.D.
Professor of Surgery, University of Texas at Houston School of Medicine, Director, Division of Immunology and Organ Transplantation, University of Texas Health Science Center at Houston, Houston, Texas

Jean Kanitakis, M.D.
Université Claude Bernard Lyon, Edouard Herriot Hospital, Lyon, France

Allan D. Kirk, M.D., Ph.D.
National Institute of Diabetes & Digestive & Kidney Diseases, National Institutes of Health, Bethesda, Maryland

David E. Kleiner, M.D.
Staff Surgical Pathologist, Laboratory of Pathology, National Cancer Institute, Bethesda, Maryland

Walter Klepetko, M.D.
Professor of Surgery, University of Vienna, Department of Cardiothoracic Surgery, Vienna, Austria

Jerzy W. Kupiec-Weglinski, M.D., Ph.D.
Professor of Surgery, David Geffen School of Medicine at UCLA, Division of Liver and Pancreas Transplantation, Department of Surgery, Los Angeles, California

Marco Lanzetta, M.D.
Director, Hand Surgery & Reconstructive Surgery, San Gerardo Hospital, Monza, Italy

W. P. Andrew Lee, M.D.
Professor of Surgery and Orthopedic Surgery, Chief, Division of Plastic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

David M. Levi, M.D.
Assistant Professor of Clinical Surgery, University of Miami, Division of Transplant Surgery, Jackson-Memorial Hospital, Miami, Florida

Gerald S. Lipshutz, M.D., D.D.S., M.S.
Assistant Professor of Surgery, David Geffen School of Medicine at UCLA, Departments of Surgery and Urology, UCLA Medical Center, Los Angeles, California

Robert R. Lorenz, M.D.
Assistant Professor of Surgery, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Section Head, Head & Neck Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio

Susan E. Mackinnon, M.D.
Shoenberg Professor of Surgery, Washington University School of Medicine in St. Louis Chief, Division of Plastic and Reconstructive Surgery, Washington University Medical Center, St. Louis, Missouri

Pedro Mancias, M.D.
Division of Pediatric Nephrology, Department of Pediatrics, University of Texas Health Science Center at Houston, Houston, Texas

Eddie Manning, M.D.
Resident, General Surgery, Department of Surgery, University of Miami, Miller School of Medicine, Miami, Florida

Samir Mardini, M.D.
Division of Plastic Surgery, Department of Surgery, Mayo Clinic College of Medicine, Rochester, Minnesota

Raimund Margreiter, M.D.
Surgical Director, Department for Transplantation Surgery, Medical University of Innsbruck, Innsbruck, Austria

Steven Marra, M.D.
Assistant Professor, Division of Cardiothoracic Surgery, Department of Surgery, Robert Wood Johnson Medical School, Cooper University Hospital, Camden, New Jersey

Gabriel M. Marta, M.D.
Department of Cardiothoracic Surgery, Medical University of Vienna, Vienna, Austria

Serge A. Martinez, M.D., J.D.
Professor of Surgery, University of Louisville School of Medicine, Division of Otolaryngology-Head and Neck Surgery, Department of Surgery, Louisville, Kentucky

Martha S. Matthews, M.D.
Associate Professor of Surgery, Head, Division of Plastic Surgery, Department of Surgery, Robert Wood Johnson Medical School, Cooper University Hospital, Camden, New Jersey

Emmanuel Morelon, M.D., Ph.D.
Division of Kidney Transplantation, Department of Surgery, Université Claude Bernard, Hôpital Edouard Herriot, Lyon, France

Joseph E. Murray, M.D.
Nobel Prize Winner, 1990, Professor of Surgery Emeritus, Harvard Medical School, Boston, Massachusetts

Peter C. Neligan, M.D.
Professor of Surgery, University of Toronto School of Medicine, Head, Division of Plastic Surgery, Toronto General Hospital, Toronto, Canada

Marina Ninkovic, M.D.
Department of Plastic and Reconstructive Surgery, Ludwig Boltzmann Institute for Quality Control, Leopold-Franzens University, Innsbruck, Austria

Waldemar L. Olszewski, M.D.
Professor of Surgery, Polish Academy of Sciences, Department of Surgical Research and Transplantology, Medical Research Center, Central Clinical Hospital, Ministry of Internal Affaires, Warsaw, Poland

Earl Owen, M.D.
Microsearch Foundation of Australia, Outer Sydney Hand and Microsurgery Unit, Sydney, Australia

Francois Petit, M.D.
Professor of Surgery, University Patis-XII, Department of Plastic Surgery, Hospital Henri-Mondor, Créteil, France

Palmina Petruzzo, M.D.
Hand Surgery and Reconstructive Microsurgery, San Gerardo Hospital, Monza-University, Monza, Italy

Rajen Ramsamooj, M.D.
Associate Professor, U.C.-Davis School of Medicine, Director of Transplant Pathology, Department of Pathology, Sacramento, California

Christopher C. Reynolds, M.D.
University of Louisville, Division of Plastic Surgery Research, Louisville, Kentucky

Justin M. Sacks, M.D.
Research Fellow, Division of Plastic Surgery, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Chris J. Salgado, M.D.
Assistant Professor of Surgery, Division of Plastic Surgery, Department of Surgery, Robert Wood Johnson Medical School, Cooper University Hospital, Camden, New Jersey

Stefan Schneeberger, M.D.
Research Assistant Professor of Surgery, Division of Plastic Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania

Joseph Serletti, M.D.
Professor of Surgery, University of Pennsylvania School of Medicine, Chief, Division of Plastic Surgery, Department of Surgery, Hospital of The University of Pennsylvania, Philadelphia, Pennsylvania

Maria Siemionow, M.D., Ph.D., D.Sc.
Professor of Surgery, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Director of Plastic Surgery Research, Head, Microsurgery Training, The Cleveland Clinic Foundation, Cleveland, Ohio

Thomas E. Starzl, M.D., Ph.D.
Director, Thomas E. Starzl Transplantation Institute, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Barckley Storey, M.D.
University of Louisville, Division of Plastic Surgery Research, Louisville, Kentucky

Louise Strande, M.S.
Division of Surgical Research, Department of Surgery, UMDNJ-Robert Wood Johnson Hospital, Cooper University Hospital, Camden, New Jersey

Marshall Strome, M.D., M.S.
Professor of Surgery, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Chairman, The Head and Neck Institute, The Cleveland Clinic Foundation, Cleveland, Ohio

Hidetoshi Suzuki, M.D.
Second Department of Anatomy, Hamamatsu University School of Medicine, Shizuoka, Japan

Chau Y. Tai, M.D.
Department of Surgery, Kern Medical Center, Bakersfield, California

Judith M. Thomas, Ph.D.
Professor of Surgery, University of Alabama at Birmingham School of Medicine, Departments of Surgery and Microbiology, Birmingham, Alabama

Thomas H. Tung, M.D.
Assistant Professor of Surgery, Washington University School of Medicine, Division of Plastic and Reconstructive Surgery, Washington University Medical Center, St. Louis, Missouri

Andreas G. Tzakis, M.D., Ph.D.
Medical Director, Transplant Services, Broward General Medical Center, Fort Lauderdale, Florida

Jignesh Unadkat, M.D.
Research Fellow, Division of Plastic Surgery, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Dalibor Vasilic, M.D.
University of Louisville, Louisville, Kentucky

Esther Voegelin, M.D.
Department of Orthopaedic Surgery, University of Bern, Inselspital, Bern, Switzerland

Osborne Wiggins, Ph.D.
Department of Philosophy, University of Louisville, Louisville, Kentucky

Section I

Chapter 1
The Establishment of Composite Tissue Allotransplantion as a Clinical Reality

Joseph E. Murray*

1.1 Introduction

My rewarding career has combined two major professional disciplines, plastic/reconstructive surgery and transplantation biology. This chapter discusses my connection to these two specialties and my fascination with composite tissue allotransplantation (CTA).

Now in my 88th year, I am eager to keep up with current surgical techniques as in the case of CTA. As Stuart Brand said, "Once a new technology rolls over you, if you're not part of the steamroller, you are part of the road."

I, as in the case of many of my colleagues, do not wish to spend the rest of our lives being part of the road. As I demonstrated throughout my career, we as plastic surgeons are in the position to make significant biological advances.

A recent issue of *Plastic and Reconstructive Surgery* featured an article entitled "Face transplantation: an extraordinary case with lessons for ordinary practice."* This face transplant operation was performed in September 2005 by Dr. Dubernard and his team in France. This partial face allotransplant represents a giant step forward in both the area of CTA and modern surgical technique. Personally, it represents the ultimate merging of plastic/reconstructive surgery and transplantation biology, which again, are the two major professional disciplines of my career.

Face transplantation has been much discussed in the current literature, encompassing both praise and criticism. Dr. Dubernard and colleagues thankfully presented their work in Tuscon, Arizona in January 2006. Dr. Thomas Starzl and Sir Roy Calne were just two of the many illustrious attendees to applaud Dubernard's work.

Dr. Dubernard, who worked in our laboratory at the Harvard Medical School, has now advanced CTA towards unexpected directions. I feel whole-heartedly that these advances are worth pursuing!

When I entered the Harvard Medical School in 1940, my plan upon graduation was to return home to mid-Massachusetts as a general surgeon. When World War II intervened, medical students were unexpectedly drafted. Surgical internship, at

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*Presented, in part, at the 75th annual meeting of the American Society of Plastic Surgeons, October 8th, 2006.

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this time, had been reduced to 9 months. My first permanent assignment was to the Valley Forge Army Hospital in Phoenixville, Pennsylvania. It was there that I treated battle causalities from Europe, Africa and the Pacific.

It was at Valley Forge where I first saw a severely burned Air Force pilot named Charles Woods. He was the first patient I ever cared for, whose life was saved and whose face was reconstructed by using tissues from another person.

Included is a picture of Mr. Woods before his terrible injury and then after multiple surgeries (Fig. 1.1). This event would serve as my first introduction into the world of transplantation biology. In addition, Charles Woods went on to become a successful business entrepreneur, politician and father.

When I returned to Boston in 1951, we began studying human skin grafts. There was a patient (c. 1952) cared for at the Chelsea Naval Hospital. She had extensive third degree burns over her entire body, requiring the use of both skin allografts and autografts. Here we are placing allografts into position (Fig. 1.2) Soon after, the autografts survived and expanded while the allografts melted away (Fig. 1.3).

This patient went on to heal completely without any contractures, presumably due to the survival of dermal remnants from the allografts. This was an important physiological discovery. Unexpectedly, we also found normal breast development, a salutary biological observation (Fig 1.4).

After World War II, the study of composite tissue transplantation expanded tremendously and began to embrace multiple disciplines. It was mainly because skin grafts were frequently and commonly used in design of experimental methodology that plastic surgeons were mainly those involved.

Around 1951, Dr. Brad Cannon became the first chairman of the American College of Surgeon's Plastic Surgical Forum Committee (Fig.1.5). He gathered together several related subject areas, including the surgical treatment of congenital deformity, cleft lip and palate, hypospadius, wound healing and skin cancers.

In the early 1950s, there was also confusion about what to call various kinds of skin grafts. Zoologist, Sir Peter Medawar clarified our terminology into familiar

Fig. 1.1 Photographs of Charles Woods before and after his severe burn injury

Fig. 1.2 Patient with extensive third degree burn

terms; those being autograft, allograft, and isograft. At that time, there was no existing medical journal dedicated solely to transplantation. Enthusiasts in tissue and organ transplantation had extreme difficulty in finding venues for publishing their material. Reports were scattered in embryology, anatomy, physiology and histology journals and symposia. Accordingly, the editors of *The Journal of Plastic Surgery* decided to include transplantation papers as an added bulletin in their journal. This continued for 10 years (Fig.1.6). The three editors at this time were Herbert Conway (Plastic surgeon, NY hospital), Ernest Eichwald (Pathologist, Great Falls, Montana), and Nathan Kaliss (Geneticist, Bar Harbor, Maine). In the 1970s, with the spectacular increase in transplantation, an independent journal, called the *American Journal of Transplantation*, was started. Today this journal is fourth among American surgical citations.

Since the first successful kidney transplant in 1954, hundreds of thousands of transplants have been performed worldwide. These include transplants of skin,

Fig. 1.3 Multiple autografts and allografts

bone and cartilage, cornea, endocrine glands, blood vessels, whole organ clusters and most impressively, composite tissue allografts. This growing field incorporates many disciplines, such as tissue engineering, oncology, genetics and immunology.

Some of the pioneering plastic surgeons involved in transplantation include John Converse, who was the second president of the transplantation society, J. Herbert Conway, and Fernando Monastario. Others include nationally recognized burn expert Truman Blocker who practice in Galveston, Texas. Lyndon Peer (Newark, New Jersey) published one of the first books on transplantation, while Bernard Sarnat became an expert in cartilage transplantation in southern California. John Woods became the first plastic surgical Chief and head of transplantation at the Mayo Clinic. Milt Edgerton and his wife, zoologist Patricia Edgerton, performed experimental work on transplantation at the Johns Hopkins Hospital.

Blair Rogers, Richard Stark, Peter Randall, and Erle Peacock were all clinical plastic surgeons performing transplantation experiments. This period was an exhilarating time. The war was now over and we were free to pursue our curiosity

Fig. 1.4 Normal breast development without contractures following skin grafting for extensive third degree burns

and professional goals (Fig.1.7). A rare camaraderie developed which continues to exist to this day.

Successful transplantation led to the need for new definition of "death" based on the loss of brain function. It also led to the increased participation of the public and media in ethical decision-making in relation to the use of living donors.

During our original transplant operations, we conferred with physicians from other hospitals, lawyers, clergy of all denominations and the general public. We approached the Dean of Harvard medical school with aspirations to set up a

Fig. 1.5 Picture of Dr. Brad Cannon

Fig. 1.6 Transplantation papers added as a bulletin to the Journal of Plastic Surgery

commission to define death in terms of loss of brain function, rather than loss of respiratory or cardiac activity. This commission report was published in the *Journal of the American Medical Association* (*JAMA*) in the late 1960s and these standards have been used nationally ever since.

From the 1950s to 1980s, I continued to work with skin grafts in mice, rabbits, dogs and human volunteers. This picture (Fig. 1.8) from 1955 shows four postage

Fig. 1.7 Some pioneering plastic surgeons

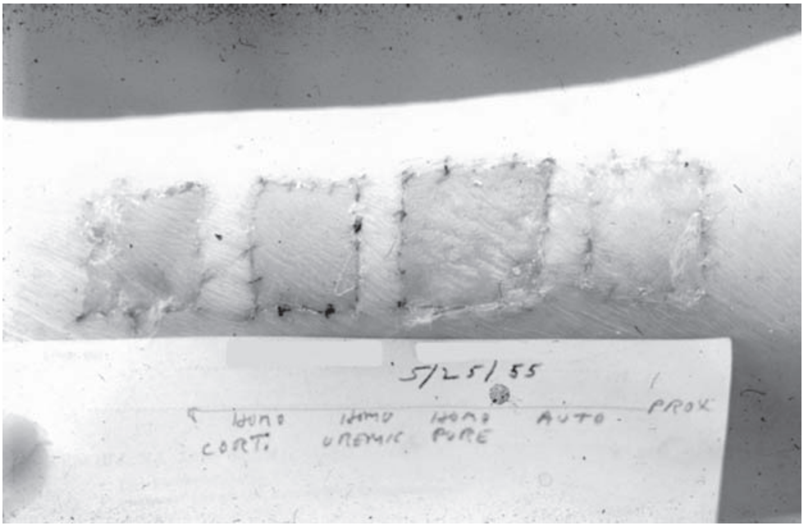

Fig. 1.8 Skin grafts to the upper arm of a uremic patient. From far right: autograft, pure homograft, from another uremic patient, from a patient on steroids

stamp-size grafts applied to the upper arm of a uremic patient. To the far right is the autograft. The second from the right is a pure homograft. The third from the right is from another uremic patient. Finally, the far left skin graft is from a patient on steroids due to another pre-existing medical condition. From these experiments, we learned that there is a differential strength of immune rejection.

In 1959, we were still testing the strength of the immune response in uremic patients. On the left (Fig. 1.9), we see the uremic twin's forearm. It shows a well-healed allograft received from his fraternal (dizygotic) healthy twin. On the right

Fig. 1.9 Forearms of the uremic patient's twin brother with skin graft from dizygotic healthy twin on right forearm and from sick uremic patient on the left forearm

side we see the healthy twin's forearm showing acute rejection of the allograft received from his sick twin brother, indicating that they were not identical twins.

The kidney transplant from the healthy-to-sick twin was performed after subjecting the uremic patient to total body irradiation to suppress his immune response. The kidney transplant was successful, and it was the first successful kidney transplant between brothers.

We also experimented with maternal skin allografts, mother-to-child. Figure 1.10 (picture taken in 1958) shows the daughter's arm with a homograft from her mother on the right and an autograft on the left. This photograph was taken on the seventh postoperative day.

Figure 1.11 shows the mother and daughter grafts 2 years later, showing thinning of the allograft without contracture. Four years later in 1961, the homograft on the right is still intact but now thinner in respect to the autograft. We now learned that maternal allografts can last longer and survive well, but not completely (Fig. 1.12).

Figure. 1.13 (picture taken in 1963) shows me at the Harvard Medical School with four dogs, all of which underwent solitary kidney transplants. These renal allografts all survived over 1 year using immunosuppressive drugs.

Possibly, the best summation of the current status of CTA is a report in the June, 2006 issue of the *American Journal of Transplantation* entitled "Bilateral hand transplantation: six years after the first case." This report represents advancement in microsurgery, successful regeneration of nerves and muscles of the hand and the

Fig. 1.10 Mother to daughter skin allograft. Right: from mother. Left: autograft

Fig. 1.11 Mother to daughter skin allograft. 2 years later

Fig. 1.12 Mother to daughter skin allograft. 4 years later

Fig. 1.13 Dr. Murray with 4 dogs who underwent solitary kidney transplants

complete healing of allogeneic skin. It also discusses the difficulty of implementing life-long immunosuppression for nonlethal conditions.

The past was great and the future will be even more exciting. I wish that I could be with you all – I will be with you in spirit on that wonderful steamroller ride! Thank you.

"Once a new technology rolls over you, if you're not part of the steamroller, you are part of the road." Stewart Brand, Amer J Transp, September 2006.

Chapter 2
The Evolution of Composite Tissue Allotransplantation: the Twentieth Century Realization of "Cosmas and Damian"

Chad R. Gordon, Joseph M. Serletti, Kirby S. Black, and Charles W. Hewitt

Abstract The purpose of this article is to review the historical background and clinical status of composite tissue allotransplantation and to discuss the scientific evolution of composite tissue allotransplantation.

Composite tissue allotransplantation rapidly progressed in the 1980s with the discovery of cyclosporine. Although most success has been achieved with hand transplantation, others have made progress with allografts of trachea, peripheral nerve, flexor tendon apparatus, vascularized knee, larynx, abdominal wall, and most recently, partial face.

As a symbol of great success, the world's first partial face allotransplantation occurred in November 2005 in France. In April 2006, the second was performed in China. There are now multiple institutions with plans to attempt the world's first full facial/scalp transplant.

Composite tissue allotransplantation offers a viable alternative for unfortunate individuals suffering severe disfigurement and is a product of many decades of experimental research, beginning with rat hindlimb allografts.

2.1 Historical Background

Composite tissue allotransplantation (CTA) involves "transplanting a graft, composed of a variety of heterogeneous antigenic tissues, across a genetic mismatch," as in the case of a hand (i.e. skin, muscle, bone, tendon, nerve, vessels). This challenge presents multiple barriers and complexities in comparison to a more homogeneous organ such as kidney or liver.

The first historical mention of CTA dates back to the year AD 348, where legend has it that twin brothers from Arabia, Saints Cosmas and Damian (circa AD 286), posthumously transplanted an Ethiopian Moor's limb in place of an elder's amputated gangrenous limb.[1] According to Jacques de Vorágine's (XIII century, AD 1270) manuscript entitled "Leyenda Aúrea de la vida de los Santos" (Aureus Legend of the Saints life), "…the guard in charge of taking care of the temple dedicated to both Saints, suffered enormously because of a tumor in his leg; and one morning

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he woke up without pain and with a leg obtained from the corpse of a Ethiopian gentleman who passed away the day before (Fig. 2.1)."

The milestones achieved in transplantation of solid organs (primarily kidney and heart) motivated surgeons in 1964 to attempt the world's first hand transplant.[2,3] This unprecedented surgery was performed by a team led by Robert Gilbert in Ecuador on a young male patient who had lost both hands in an explosion. Immunosuppressive options were limited to azathioprine and hydrocortisone. Unfortunately, severe rejection to the hand was present 2 weeks after surgery and re-amputation was indicated soon thereafter. A trial of increment doses of immunosupression was not advised since previous animal experiments demonstrated severe toxicity.[4] This complication delayed the clinical dream of hand transplantation and decades would pass before the next attempt.

During this same year, the first clinical trials by Calne began using cyclosporine (CsA) in renal, pancreatic and liver transplantation.[5–7] Once the clinical efficacy of CsA had been demonstrated in solid organ transplantation, multiple research teams began investigating limb allograft transplant models in rats, dogs and rabbits. It was Hewitt (1985) who provided the groundbreaking results demonstrating successful rat limb allotransplants with CsA.[8–10]

These rat limb allografts showed a significant improvement in mean survival time with CsA during a period of 20 days (101 versus 18 days). Higher acceptance rates were subsequently reported when using a maintenance dose of CsA twice-per-week for in-definitive time (400 days survival). It was also shown that the transplanted limb's marrow and stroma functioned as a new type of bone marrow transplant, resulting in immune chimerism and potential tolerance induction without graft-versus-host disease (GVHD).[11]

Fig. 2.1 Saints Cosmas and Damian performing a posthumous limb allograft transplant. (With permission from Gordon CR, Nazzal J, Lozano-Calderan SA, et al. "From experimental rat hindlimb to clinical face composite tissue allotransplantation: historical background and current status." Microsurgery 26(8):566–72, 2006.) (*See Color Plates*)

Many studies followed some tested combinations of steroids and CsA, while others evaluated different routes of administration. Most transplant researchers at this time were convinced that CsA was effective in avoiding limb allograft rejection in rats.[12–14] It was at this time, that the potential option of "using allografts of facial structures" was introduced by Achauer and colleagues in 1985.[15]

In 1987, Gunman-Stein and Shons confirmed the advantages of CsA by transplanting immature limbs in rats. These allografts experienced significant recovery of posterior limb function.[16] Kniha (1989) further demonstrated an acceptable limb growth rate while using CsA in a similar model in rabbits.[17] These investigational accomplishments not only confirmed adequate tissue integration of CsA, but also demonstrated the unexpected recovery of function and tissue growth.[18]

Pharmalogical research continued and new drugs were soon added to the list of available immunosuppressive agents. These included FK-506 (tacrolimus) and mycophenolate mofetil (MMF). In 1993, Benhaim demonstrated that rat limb allotransplants treated with MMF did not suffer rejection up to 32 weeks, versus those who had received CsA having mild-to-moderate acute graft rejection within 6 months. In addition, these limb allografts recovered full sensation and partial motor function.[19]

Three years later, the same group demonstrated more impressive postoperative limb function with the combination of both MMF and CsA. Again in 1999, they tested the combination of tacrolimus and MMF versus CsA and showed the former combination provided a superior antirejection effect without significant toxicity.[20]

By 2003, Siemionow provided the first and only rat transplant model to achieve life-long (720 days) donor-specific tolerance using fully major histocompatibility-mismatched hindlimb allografts. The immunosuppression was limited to a 7-day protocol of anti-alpha/beta T-cell receptor monoclonal antibody and CsA.[21–23]

In September 1991, Hewitt and Black co-chaired a conference sponsored by the Service for Rehabilitation Research and Development (a division of the Department of Veterans Affairs) held in Seattle, Washington. Its purpose was to entertain the feasibility of extremity (CTA) transplantation in patients with limb loss. Attendees concluded that the clinical reality of limb transplantation was quite possible, and many, in fact, expected the first attempts at hand transplantation to occur within the next 5 years.[24]

Six years later, in November 1997, the second conference was held in Louisville, Kentucky, known as the *First International Symposium on Composite Tissue Transplantation*. Various surgeons and transplant immunologists from around the world gathered to discuss numerous ethical, clinical, and research dilemmas in relation to hand transplantation.[25,26]

It was not until the researchers at Louisville released their (1998) revolutionary work demonstrating for the first time, in large animal CTA experimentation, that graft rejection could be prevented (including skin) using a clinically relevant immunosuppressive protocol consisting of cyclosporine and MMF. This achievement immediately called into question previous results which showed graft rejection in primate models and the validity of the primate model in representing composite