Intestinal Failure

Diagnosis, Management and Transplantation

Intestinal Failure

Diagnosis, Management and Transplantation

EDITED BY

Alan N. Langnas, DO
Chief, Section of Transplant Surgery
University of Nebraska Medical Center
Omaha, Nebraska, USA

Olivier Goulet, MD, PhD
Pediatric Gastroenterology-Hepatology and Nutrition
Reference Center for Rare Digestive Diseases
Integrated Program of Intestinal Failure, Home Parenteral Nutrition
and Intestinal Transplantation
University of Paris-Descartes
Necker Hospital
Paris, France

Eamonn M.M. Quigley, MD, FRCP, FACP, FACG, FRCPI
Alimentary Pharmabiotic Centre
Department of Medicine
National University of Ireland, Cork
Cork, Ireland

Kelly A. Tappenden, PhD, RD
Department of Food Science and Human Nutrition
University of Illinois at Urbana-Champaign
Urbana, Illinois, USA

Blackwell
Publishing

Blackwell Publishing, Inc., 350 Main Street, Malden, Massachusetts 02148-5020, USA
Blackwell Publishing Ltd, 9600 Garsington Road, Oxford OX4 2DQ, UK
Blackwell Publishing Asia Pty Ltd, 550 Swanston Street, Carlton, Victoria 3053, Australia

First published 2008
1 2008

Library of Congress Cataloging-in-Publication Data

Intestinal failure : diagnosis, management and transplantation / edited by Alan Langnas . . . [et al.].
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4051-4637-1
1. Intestines–Diseases. I. Langnas, Alan.
[DNLM: 1. Intestines–physiopathology. 2. Intestinal Diseases–drug therapy.
3. Intestinal Diseases–surgery. 4. Intestines–transplantation. WI 400 I6022 2008]
RC860.I59 2006
616.3'4–dc22
2007015740
ISBN: 978-1-4051-4637-1

A catalogue record for this title is available from the British Library

Set in 8.75/12pt Meridien by Aptara Inc., New Delhi, India
Printed and bound in Singapore by Fabulous Printers Pte Ltd

Commissioning Editor: Alison Brown
Editorial Assistant: Jennifer Seward
Development Editor: Elisabeth Dodds
Production Controller: Debbie Wyer

For further information on Blackwell Publishing, visit our website:
http://www.blackwellpublishing.com

Contents

List of Contributors

Kareem M. Abu-Elmagd, MD, PhD, FACS
Professor of Surgery
Director, Intestinal Rehabilitation and Transplantation Center
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania, USA

Ahmed Abu-Shanab, MB BCh, MSc (internal medicine)
Alimentary Pharmabiotic Centre
Department of Medicine
National University of Ireland, Cork
Cork, Ireland

Sue V. Beath, BSc, MRCP, FRCPCH
Consultant Paediatric Hepatologist
Birmingham Children's Hospital
West Midlands, UK

Enrico Benedetti, MD, FACS
Professor and Head, Department of Surgery
University of Illinois at Chicago
Chicago, Illinois, USA

Jean F. Botha, MBBCh, FCS(SA)
Assistant Professor
Department of Surgery
Section of Transplantation
University of Nebraska Medical Center
Omaha, Nebraska, USA

Alan L. Buchman, MD, MSPH
Professor of Medicine and Surgery
Feinberg School of Medicine
Division of Gastroenterology
Northwestern University
Chicago, Illinois, USA

Brenda Bursch, PhD
Professor of Psychiatry and Biobehavioral Sciences, and Pediatrics
David Geffen School of Medicine at UCLA
Los Angeles, California, USA

Virginie Colomb, MD, PhD
Pediatric Gastroenterology-Hepatology and Nutrition
Reference Center for Rare Digestive Diseases
Integrated Program for Intestinal Failure, Home Parenteral Nutrition and Intestinal Transplantation
University of Paris-Descartes
Necker Hospital
Paris, France

Anthony J. Demetris, MD
Starzl Professor of Transplant Pathology
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania, USA

John K. DiBaise, MD
Associate Professor of Medicine
Mayo Clinic
Scottsdale, Arizona, USA

Carlo Di Lorenzo, MD
Professor of Clinical Pediatrics
Division of Pediatric Gastroenterology
The Ohio State University and Columbus Children's Hospital
Columbus, Ohio, USA

Christopher Duggan, MD, MPH
Associate Professor of Pediatrics, Harvard Medical School
Medical Director, Short Bowel Syndrome Program
Children's Hospital, Boston
Boston, Massachusetts, USA

Roger W. Evans, PhD
Consultant in Health Care
Rochester, Minnesota, USA

Douglas G. Farmer, MD
Associate Professor of Surgery
Director, Intestinal Transplant Program
Dumont-UCLA Transplant Center
Los Angeles, California, USA

Erin M. Fennelly, RD, CNSD
Georgetown University Transplant Institute
Washington, DC, USA

Yigael Finkel, MD, PhD
Associate Professor of Paediatrics
Department of Woman and Child Health
Karolinska Institutet
Stockholm, Sweden

Thomas Fishbein, MD
Professor of Surgery and Pediatrics
Director, Intestinal and Pediatric Liver Transplantation
Georgetown University Hospital
Washington, DC, USA

Alison Freifeld, MD
Director, Immunocompromised Host Infectious Diseases Program
Associate Professor
Department of Medicine
University of Nebraska Medical Center
Omaha, Nebraska, USA

Jonathan P. Fryer, MD
Associate Professor of Surgery
Director, Intestinal Transplantation
Feinberg School of Medicine
Northwestern University
Chicago, Illinois, USA

Simon M. Gabe, MSc, MD, FRCP
Consultant Gastroenterologist and Honorary Senior Lecturer
Lennard-Jones Intestinal Failure Unit
St Mark's Hospital
Harrow, UK

Raquel Garcia-Roca, MD
Department of Surgery
University of Minnesota
Minneapolis, Minnesota, USA

Jodi Gentleman, LCSW
Medical Social Worker
The Nebraska Medical Center
Omaha, Nebraska, USA

Olivier Goulet, MD, PhD
Pediatric Gastroenterology-Hepatology and Nutrition
Reference Center for Rare Digestive Diseases
Integrated Program for Intestinal Failure, Home Parenteral Nutrition and Intestinal Transplantation
University of Paris-Descartes
Necker Hospital
Paris, France

David R. Grant, MD, FRCSC
Professor of Surgery
Surgical Director, Multi-Organ Transplantation
University Health Network
University of Toronto
Toronto, Ontario, Canada

Wendy J. Grant, MD
Assistant Professor of Surgery
Organ Transplantation Program
University of Nebraska Medical Center
Omaha, Nebraska, USA

Thomas G. Gross, MD, PhD
Gordon Teter Chair for Pediatric Cancer
Associate Professor, Department of Pediatrics, The Ohio State University
Chief, Division of Hematology/Oncology/BMT, Columbus Children's Hospital
Columbus, Ohio, USA

Rainer Gruessner, MD
Professor of Chairman
Department of Surgery
University of Arizona
Tucson, Arizona, USA

Gabriel J. Hauser, MD, MBA
Vice Chairman, Department of Pediatrics
Professor of Pediatrics, Physiology and Biophysics
Medical Director, Pediatric Inpatient Services
Chief, Pediatric Critical Care and Pulmonary Medicine
Georgetown University Children's Medical Center
Washington, DC, USA

Simon P. Horslen, MB ChB, FRCPCH
Professor of Pediatrics, University of Washington
Medical Director, Liver and Intestine Transplantation
Children's Hospital and Regional Medical Center
Seattle, Washington, USA

Paul E. Hyman, MD
Professor of Pediatric Gastroenterology and Behavioral Pediatrics
University of Kansas School of Medicine
Kansas City, Kansas, USA

Dominique M. Jan, MD
Professor of Clinical Surgery
Columbia University
College of Physicians and Surgeons
New York, New York, USA

Khursheed N. Jeejeebhoy, MBBS, PhD, FRCP, FRCPC
Professor Emeritus, Department of Medicine
University of Toronto
Toronto, Ontario, Canada

Francisca Joly, MD
Gastroenterology and Nutrition Support
Reference Centre for Rare Digestive Diseases
Integrated Program for Intestinal Failure, Home Parenteral Nutrition and Intestinal Transplantation
Hôpital Beaujon
Clichy la Garenne, France

Andre Kalil, MD
Department of Medicine
University of Nebraska Medical Center
Omaha, Nebraska, USA

Daniel S. Kamin, MD
Division of Gastroenterology and Nutrition
Children's Hospital, Boston
Boston, Massachusetts, USA

Stuart S. Kaufman, MD
Medical Director
Pediatric Liver and Intestinal Transplantation
Georgetown University Transplant Institute and
Children's National Medical Center
Washington, DC, USA

Sanja Kolaček, MD
Professor of Pediatrics
Head, Division of Pediatrics
Chief, Referral Center for Pediatric Gastroenterology and Nutrition
Children's Hospital Zagreb
Zagreb University Medical School
Zagreb, Croatia

Alan N. Langnas, DO
Chief, Section of Transplant Surgery
University of Nebraska Medical Center
Omaha, Nebraska, USA

Henri G. Leuvenink, PhD
Head of Surgical Research Laboratory
University Medical Center Groningen
University of Groningen
Groningen, The Netherlands

Marc S. Levin, MD
Associate Professor of Medicine
Division of Gastroenterology
Washington University School of Medicine; and
Staff Physician
St Louis VA Medical Center
St. Louis, Missouri, USA

Greger Lindberg, MD, PhD
Associate Professor
Department of Medicine
Division of Gastroenterology and Hepatology
Karolinska Institutet
Stockholm, Sweden

David A.J. Lloyd, MA, MRCP
Lennard-Jones Intestinal Failure Unit
St Mark's Hospital
Harrow, UK

Frances R. Malone, RN, ARNP, PhD
Division of Transplant Surgery
Children's Hospital and Regional Medical Center
Seattle, Washington, USA

Bernard Messing, MD, PhD
Gastroenterology and Nutrition Support
Reference Centre for Rare Digestive Diseases
Integrated Program for Intestinal Failure, Home Parenteral Nutrition
and Intestinal Transplantation
Hôpital Beaujon
Clichy la Garenne, France

Julije Meštrović, MD, PhD
Assistant Professor of Pediatrics
Head, Pediatric Intensive Care Unit
Spit University Hospital
Split, Croatia

Hayat Mousa, MD, FAAP
Medical Director, Center for Advanced Research in
Neuromuscular Gastrointestinal Disorders (C.A.R.I.N.G)
Associate Professor in Clinical Pediatrics, Division of
Gastroenterology
The Ohio State University College of Medicine and Public Health
Columbus, Ohio, USA

Kenneth A. Newell, MD, PhD
Professor of Surgery
Department of Surgery and the Emory Transplant Center
Emory University
Atlanta, Georgia, USA

Vincent B. Nieuwenhuijs, MD, PhD
Abdominal and Transplant Surgery
University Medical Center Groningen
Groningen, The Netherlands

Mihai Oltean, MD
Department of Surgery and Transplantation
Sahlgrenska University Hospital
Gothenburg, Sweden

Liam O'Mahony, BSc, PhD
Principal Investigator
Alimentary Pharmabiotic Centre
BioSciences Institute
University College Cork
Cork, Ireland

Fabrizio Panaro, MD
Division of Transplantation
University of Illinois at Chicago
Chicago, Illinois, USA

Leonard W. Penkoski, MSW, CSW
University of Nebraska Medical Center
Omaha, Nebraska, USA

Rutger J. Ploeg, MD, PhD
Professor of Surgery
Abdominal and Transplant Surgery
University Medical Center Groningen
Groningen, The Netherlands

Jeffrey S. Plotkin, MD
Associate Professor of Anesthesia and Surgery
Director, Transplant Anesthesia and Critical Care
Georgetown University Hospital
Washington, DC, USA

Rodrigo Quera, MD
Department of Internal Medicine
Gastroenterology
Hospital Clinico Universidad de Chile
Santiago de Chile, Chile

Eamonn M.M. Quigley, MD, FRCP, FACP, FACG, FRCPI
Alimentary Pharmabiotic Centre
Department of Medicine
National University of Ireland, Cork
Cork, Ireland

Deborah C. Rubin, MD
Professor of Medicine Molecular Biology
and Pharmacology
Washington University School of Medicine
St. Louis, Missouri, USA

Harry C. Sax, MD
Professor of Surgery
The Warren Alpert Medical School of
Brown University
Surgeon-in-Chief
The Miriam Hospital
Providence, Rhode Island, USA

Shimul A. Shah, MD
Assistant Professor of Surgery
Division of Organ Transplantation
University of Massachusetts Memorial Medical Center
University of Massachusetts Medical School
Worcester, Massachusetts, USA

James H. Sorrell, MD
Associate Professor
Department of Psychiatry
Nebraska Medical Center
Omaha, Nebraska, USA

Debra Sudan, MD
Professor of Surgery
Director, Intestinal Rehabilitation Program
University of Nebraska
Omaha, Nebraska, USA

Kelly A. Tappenden, PhD, RD
Department of Food Science and Human Nutrition
University of Illinois at Urbana-Champaign
Urbana, Illinois, USA

Giuliano Testa, MD, FACS
Associate Professor of Surgery
Director, Liver Transplantation and Hepatobiliary Surgery
University of Chicago Medical Center
Chicago, Illinois, USA

Jon S. Thompson, MD
Professor of Surgery
University of Nebraska Medical Center
Omaha, Nebraska, USA

Clarivet Torres, MD
Pediatric Gastroenterology – Hepatology
Liver-Intestinal Transplant
Georgetown University Hospital Children
National Medical Center
Medical Director, Intestinal Rehabilitation Program
Washington, DC, USA

Ramsey K. Umar, MD
Fellow, Divisions of Gastroenterology and Hepatology
Feinberg School of Medicine
Northwestern University
Chicago, Illinois, USA

Jon A. Vanderhoof, MD
Consultant, Division of Gastroenterology
Department of Medicine
Children's Hospital, Boston, Massachusetts, USA;
Lecturer of Pediatrics, Harvard Medical School
Boston, Massachusetts, USA; and
Vice-President, Global Medical Affairs
Mead Johnson Nutritionals
Evansville, Indiana, USA

Jennifer N. Woodard
Division of Nutritional Sciences
University of Illinois at Urbana-Champaign
Urbana, Illinois, USA

Jeremy M. Woodward, MA, PhD, FRCP
Consultant Gastroenterologist
Addenbrooke's Hospital
Cambridge, UK

Tong Wu, MD, PhD
Associate Professor of Pathology
Department of Pathology
Thomas E. Starzl Transplantation Institute
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania, USA

Rosemary J. Young, NP-C, MS, BSN
Boys Town National Research Hospital
Boys Town, Nebraska, USA

Foreword

What a privilege it is to have been a part of the greater medical community during the past fifty years; and to have had the opportunity to witness, and to have contributed in a small way to this special period of extraordinary and unprecedented discovery and advancement in virtually every aspect of basic and clinical research; and to experience the joy and satisfaction of the effective practical translation of the new knowledge and technology to the solution or amelioration of difficult and complex patient problems. Although remarkable progress has been made in the acquisition, assessment and useful application of a broad spectrum of medical knowledge, skill, experience, judgment and wisdom throughout the centuries of the past two millennia, advances in basic and clinical science, technology, health care delivery, public health, and preventive medicine during the past century have been especially unparalleled and enormous; and have greatly surpassed the total of all the knowledge in all of the disciplines related to medical and surgical endeavors throughout all previous recorded history. Each era has had its outstanding clinicians and investigators who have exhibited exceptional intellect, curiosity, courage, conscientiousness, competence, character, creativity, and vision in making significant, and often lasting, contributions to the optimal practice of the medicine and surgery of its time; and the twentieth century has produced many more such talented and productive clinically oriented scientists than any other equivalent period.

This unique volume, "Intestinal Failure; Diagnosis, Management and Transplantation," with its four able and distinguished editors who are all leading contributors to this relatively new field; and the impressive group of more than sixty-five internationally recognized additional authors who have joined them from nine countries, overtly manifests the magnitude and usefulness of the data, knowledge, and experience which have been amassed in this critically important area in a rather short time, largely as a result of multidisciplinary collaboration and cooperation. The comprehensive nature of this tome is suggested by its title and evident by its table of contents which logically and rationally groups its forty-two chapters into seven parts, covering virtually the full range of the field of intestinal failure from the relatively straightforward to the complex, and from the subtle to the sublime.

During the latter half of the past century, the basic laboratory development and successful clinical application of total parenteral nutrition has resulted in multiple significant changes in the modern practice of medicine, surgery and pediatrics, and many of their subspecialties. Arguably, none of the benefits of this technique have been more fundamental and lifesaving than the subsequent developments and advances in the understanding, operative procedures, and metabolic and nutritional management and support of patients with short bowel syndrome following massive intestinal resection. Moreover, primarily as a result of the remarkable salvage of most of these patients with this critically severe life-threatening situation, it was eventually recognized that a broader spectrum of disorders of alimentary tract function could be identified besides the "end game" short bowel syndrome; and that patients with these intestinal dysfunctions deserved our collective attention, investigation, and attempts to prevent, ameliorate or cure. Accordingly, the concept of intestinal failure inevitably and justifiably arose, and continues to evolve. Just as the most challenging individual pathophysiological (and frequently lethal) conditions involving the heart, lung, liver, and kidney often result in various degrees and types of failure of these organs and their associated systems, so to, it has become obvious that the relatively more extensive and expansive alimentary tract, together with its important

appendages ranging from the salivary glands to the gallbladder, liver, and pancreas, can also exhibit various manifestations of failure. Intestinal failure has had both short and lengthy definitions and will likely undergo additional revisions as knowledge of this deceptively simple yet tremendously complex and adaptable organ system, and the various failures of its multiple components, accumulates from further study. Essentially, intestinal failure is a condition characterized by deficient, inadequate, ineffective, or non-existent performance of the appropriate and expected functions essential for the safe and optimal absorption of the fluids and nutrients required to maintain the normal physiologic activities of the body cell mass.

The current strategies of nutritional and metabolic support of the whole patient and of the primary organ systems, such as the cardiovascular, respiratory, renal, hepatic, intestinal, and central nervous system, must progress and advance to the cellular and subcellular levels if the ultimate goal of providing optimal nutritional, metabolic, immunologic, pharmacologic, and interventional support for all patients under all conditions at all times is to be realized. The intricate relationships among nutrient substrates, cellular biology, immunology, and the human genome are myriad, and their identification, classification, and beneficial application to the management of complex and/or critically ill patients will undoubtedly present new frontiers for basic and clinical investigation throughout the twenty-first century and beyond. This tome explores these promising possibilities and demonstrates clearly that knowledge of, and the judicious practice of, clinical nutrition, metabolism, immunology, cell biology, genetics, and organ transplantation require the most sophisticated integration of clinical skills and acumen with the basic science disciplines of biology, chemistry, physics, genomics, immunology, pharmacology, interventional therapeutics, and hybrids of these fundamental areas.

It has been a source of immense gratification for me to have lived through a most exciting era of basic discovery and efficacious clinical application of countless modalities and technological advances of nutritional and metabolic support to the rational management of a wide variety of nutritionally deficient and/or critically ill patients in virtually all medical and surgical disciplines. Measures for reducing the morbidity and mortality associated with all major pathophysiologic conditions, and their management by improving the nutritional status of patients, have expanded vastly from the simple peripheral intravenous infusion of isotonic carbohydrate and electrolyte solutions to the complex and sophisticated parenteral and enteral provision of most or all of the nutrient requirements in myriad clinical situations during my professional lifetime of more than four decades. Today, clinical nutrition is advancing rapidly toward the provision of optimal nutrient substrates to individual cells or groups of cells, whether normal or compromised, and in reality represents the practice of clinical biochemistry. The continuing identification and classification of genetic control of all metabolic events in human beings is well on its way, and upon its completion, nutritional support will acquire an unprecedented degree of precision; and this molecular biologic revolution will transform the practice of medicine and surgery forever. A more recent genuine and heartfelt gratification for me has been the growth and development of invaluable and productive personal and professional relationships which have been spawned by the cooperation and collaboration among basic and clinical scientists throughout the world. This volume is exemplary evidence of some of the most objective and tangible success of such mutual endeavors and serves as an outstanding model for others.

Total parenteral nutrition, inaugurated successfully as a useful basic clinical nutritional technique more than forty years ago, has been instrumental directly in saving countless lives and has demonstrated emphatically the relevance of adequate nutritional support and nutrition status to achieving optimal clinical outcomes. These results have subsequently led to the monumental increase in the development and application of enteral feedings in patients with functioning gastrointestinal tracts, but whose oral intakes were inadequate to support normal bodily structure and functions. Furthermore, the consequent obvious need for specialized ambulatory and home parenteral and enteral nutritional support has fostered and advanced the unbridled development of home health care and home nutritional support. Initially, the primary goal of total parenteral nutrition was to meet the nutritional needs of malnourished patients who could not eat, would not eat, should not eat, or could not eat enough. Patients with short bowel syndrome, regardless of the etiology, were the prototype beneficiaries of

the newly developed alternate feeding technique; and not only could they be fed adequately to survive their catastrophic condition, but they could "buy time" to allow and promote adaptation of the residual bowel to carry out normal or near normal absorptive functions. In patients who could not adapt sufficiently to reestablish adequate intestinal function, nutrient requirements unable to be met entirely by the intestinal tract could be supplemented intravenously as required. Some patients have been supported by parenteral nutrition at home for more than thirty years to date and have adapted quite well to the changes imposed on their lifestyles. On the other hand, some have had physical, psychological, emotional, and other problems including recurring sepsis, liver dysfunction, thrombosis and/or exhausted venous access, which have stimulated attempts either to undertake intensive intestinal rehabilitation measures to increase absorption using special regimens of enterocyte stimulation (growth factors) and enterocyte nutrients (glutamine) to promote optimal adaptation in order to wean patients from parenteral nutrition. Finally, when all reasonable conservative attempts to overcome or compensate for intestinal failure and its complications have proven inadequate, intestinal lengthening procedures and, ultimately, intestinal transplantation become the only viable therapeutic options at the present time. However, future innovative techniques, together with the natural maturation and modifications of medical technology and practices that are now occurring, and will continue to occur, are most exciting, promising, almost incomprehensible, and seemingly unlimited in dealing with this most challenging intestinal dilemma.

For the opportunity to contribute my thoughts through this foreword, I am grateful to the editors, who have already earned professional distinction as gifted, energetic and innovative investigators, teachers, practitioners, writers, advocates and leaders in all aspects of the vital field of nutritional support and management of intestinal failure. They have diligently and capably applied their innate and acquired qualities and talents throughout this comprehensive work product, together with their outstanding group of authors and co-authors, to provide a landmark reference book and practical manual, which will undoubtedly serve the needs of the entire range of individuals interested in providing safe, competent, integrated, and comprehensive management and support of patients with intestinal failure, from the novice students to the most experienced investigators and clinical practitioners. A unique aspect of this volume is that it concisely, and virtually completely, presents the up-to-date key information required for a thorough understanding of the full spectrum of intestinal failure from the basic fundamentals of nutritional biochemistry to the practical essentials in the successful management of the most critically ill and malnourished patients in a wide variety of conditions and situations. Thus, it can serve aptly and concurrently as a basic reference tome, as a convenient and practical handbook, and as a stimulus for anticipated innovative and ingenious future investigational endeavors.

Stanley J. Dudrick, MD, FACS
Chairman, Department of Surgery
Director, Program in Surgery
Saint Mary's Hospital/Yale University
School of Medicine
Professor of Surgery
Yale University School of Medicine

Preface

Intestinal failure is a rare, though devastating, condition that may threaten life, or seriously impair its quality, for those afflicted. These latter factors, together with the wide range of medical and surgical specialties that may become embroiled in the care of the intestinal failure patient, have led this topic to assume an importance in modern medicine that greatly exceeds that which its prevalence alone would demand. This has also been an area of tremendous clinical and research activity and much progress. Refinements in parenteral nutrition now permit long-term survival for many intestinal failure patients, while the advent of intestinal transplantation as a valid clinical option provides the hope of even greater independence. On embarking on the project we recognised a need to provide, in a single volume, an inclusive survey of the filed which encompassed advances in both basic science and clinical practice.

The goal of this volume, therefore, is to bring these developments together and in so doing to update the clinician, scientist and clinical investigator, alike, on the very latest information on the science and practice of intestinal failure and to present this in a manner that is accessible to all. We have endeavoured to provide the reader with a comprehensive survey of the pathogenesis, assessment and management of intestinal failure, in each instance providing the scientific background that underpins progress in each of these areas. Dilemmas in this area transcend science and medical practice and involve significant ethical, socio-economic and psychological issues; each is addressed to ensure a holistic approach to the topic.

We hope that this book will be your "go to" source on this topic and that it will also serve to advance understanding of the field, promote optimal patient care and stimulate further research.

Alan N. Langnas, DO
Olivier Goulet, MD, PhD
Eamonn M.M. Quigley, MD, FRCP, FACP, FACG, FRCPI
Kelly A. Tappenden, PhD, RD

Abbreviations

2-MG	2-monoacylglycerol
6-TG	6-thioguanine compounds
ACR	acute cellular rejection
ACAT	acylcoenzyme A:cholesterol acyltransferase
A.S.P.E.N.	American Society for Parenteral and Enteral Nutrition
ADCC	antibody-dependent cellular cytotoxicity
APC	antigen presenting cells
AIE	autoimmune enteropathy
BPD	biliopancreatic diversion
BINOCAR	British Isles Network of Congenital Anomaly Registers
BAL	broncho-alveolar lavage
BB	brush border
CCR9	cadherin, chemokine receptor 9
CRDs	carbohydrate recognition domains
CARD	Caspase Activation and Recruit Domain
CMS	Center for Medicare and Medicaid Services
CMS	Centers for Medicare and Medicaid Services
CVC	central venous catheter
CVT	central venous thrombosis
CCRs	chemokine receptors
CHB	Children's Hospital Boston
COG	Children's Oncology Group
CIF	chronic intestinal failure
CIP	chronic intestinal pseudo-obstruction
CART	cocaine and amphetamine regulated transcript
CFUs	colony forming units
CBC	complete blood counts
CEF	continuous enteral feeding
CDAI	Crohn's Disease Activity Index
cpm	cycles per minute
cAMP	cyclic adenosine monophosphate
CSA	cyclosporine
CMV	cytomegalovirus
CTL	cytotoxic T lymphocytes
DD	deceased donor
DC-SIGN	Dendritic Cell Specific ICAM-3-Grabbing Non-integrin
DC	dendritic cells
DNA	deoxyribonucleic acid
DG	diacylglycerol
DRG	diagnosis-related group
DPP IV	dipeptidyl peptidase IV
DGBP	distal gastric bypass
DXA	dual-energy X-ray absorptiometry
EBER	EBV encoded RNA
EBV-CTLs	EBV-specific cytotoxic T-cells
EM	electron microscopic
ESLD	end-stage liver disease
ENS	enteric nervous system
EGF	epidermal growth factor
EBV	Epstein-Barr Virus
EGD	esophagogastroduodenoscopy
EVA	ethyl vinyl acetate plastic
ESBLs	extended-spectrum beta-lactamases
EJV	external jugular vein
ECM	extracellular matrix
FAE	follicle associated epithelium
FFA	free fatty acids
FGID	functional gastrointestinal disorders
GBP	gastric bypass
GIST	gastrointestinal stromal tumors
GJ	gastro-jejunal
GF	germ-free
GLP2	glucagon-like peptide-2
Gln	glutamine
GVHD	graft-vs-host-disease
GH	growth hormone
GALT	gut-associated lymphoid tissue

HCRIS	Healthcare Cost Reporting Information System
HO-1	hemoxygenase-1
HSPG	heparan sulfate proteoglycan
HTK	Histidine-Triptophane-Ketoglutarate
HD	Hodgkin's disease
HPN	home parenteral nutrition
hRFC	human reduced folate carrier
hTHTR-1	human thiamine transporter-1
HES	hydroxy-ethyl starch
IC-DMP	ICCs of the deep muscular plexus
IRAKs	IL-1R associated kinases
IRAK-M	IL-1R-associated kinase M
IBAT	ileal bile acid transporter
ICV	ileocecal valve
IPEX	immune dysregulation, polyendocrinopathy autoimmune enteropathy X-linked
IgA	immunoglobulin A
IMA	inferior mesenteric artery
IVC	inferior vena cava
IBD	inflammatory bowel disease
IGF-1	insulin-like growth factor 1
IGF-2	insulin-like growth factor 2
IL-2	interleukin-2
IJV	internal jugular vein
ICC	interstitial cells of Cajal
IFALD	intestinal failure associated liver disease
IF	intestinal failure
ITR	Intestinal Transplant Registry
ITx	intestinal transplantation
IDI	intractable diarrhea of infancy
IELs	intra-epithelial lymphocytes
IR	ischemia- and reperfusion
I-ITx	isolated intestinal transplantation
iLTx	isolated liver transplant
JIB	jejunoileal bypass
KGF	keratinocyte growth factor
LMP	latent membrane protein
LPS	lipolysaccharidases
L-ITx	liver intestinal transplantation
LD	living donor
LDITx	living donor segmental intestinal transplants
LCTs	long chain triglycerides
MEDPAR	Medicare Provider Review and Analysis
MCTs	medium chain triglycerides
MMIHS	megacystis microcolon intestinal hypoperistalsis syndrome
MLNs	mesenteric lymph nodes
MVT	mesenteric venous thrombosis
MSSA	methicillin-susceptible organisms
MTP	microsomal triglyceride transfer protein
MVA	microvillous atrophy
MMC	migrating motor complex
MNGIE	mitochondrial neurogastrointestinal encephalomyopathy
MAP	mitogen activated protein
mMVTx	modified multivisceral transplantation
MALT	mucosa-associated lymphoid tissue
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MODS	multi-organ dysfunction syndrome
MVT	multivisceral transplant
MVTx	multivisceral transplantation
MMF	mycophenolate mofetil
MyD88s	MyD88 short
NHEs	Na/Hexchangers
NBS	Narcotic Bowel Syndrome
NK	natural killer
NEC	necrotizing enterocolitis
NPC1L1	Niemann-Pick C1-like 1 protein
NPO	nil per os
NO	nitric oxide
NAFLD	non-alcoholic fatty liver disease
NHL	non-Hodgkin lymphoma
Nod	nucleotide-binding oligomerization domain
NST	nutrition support team
OASIS	Oley A.S.P.E.N. Information System
PTH	parathyroid hormone
PN	parenteral nutrition
PNAC	parenteral nutrition associated cholestasis
ppm	parts per million
PAMPs	pathogen associated molecular patterns
PRRs	pattern recognition receptors
PELD	pediatric end-stage liver disease
PYY	peptide YY
PEG	percutaneous endoscopic gastrostomy
PAS	periodic acid Schiff
PIF	permanent intestinal failure
PE	physical exam
PAF	platelet activating factor
PEG	polyethylene glycol

PCR	polymerase chain reaction
PMNs	polymorphonuclear leukocytes
PV	portal vein
PTLD	post-transplant lymphoproliferative disease
PDI	protracted diarrhea of infancy
PE	pulmonary embolism
QoL	quality of life
QALY	quality-adjusted life year
SSRIs	selective reuptake inhibitors
STEP	serial transverse enteroplasty
SCID	severe combined immune deficiency
SBS	short bowel syndrome
SCFAs	short-chain fatty acids
SILT	simultaneous intestinal and liver transplant
SIGIRR	single immunoglobulin IL-1R-related molecule
SIBO	small intestinal bacterial overgrowth
SMVT	sodium-dependent multivitamin transporter
SVCT-1	sodium-dependent vitamin C transporter 1
subCVs	subclavian vein
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SVC	superior vena cava
SOCS1	suppressor of cytokine signaling 1
TCR	T cell receptor
TPMT	thiopurine methyltransferase
TRIF	TIR-domain-containing adaptor protein inducing interferon
TIRAP	TIR-domain-containing adaptor protein
TIR	toll/interleukin-1 receptor
TLRs	toll-like receptors
TPN	total parenteral nutrition
TGF-α	Transforming growth factor-α
TA	transit-amplifying
ITx	transplantation of any intestine inclusive graft
TG	triacylglycerols
TRAM	TRIF-related adaptor molecule
TRAIL	tumor necrosis factor related apoptosis inducing ligand
TNF-α	tumor necrosis-factor alpha
UNOS	United Network for Organ Sharing
UW	University of Wisconsin solution
VRE	vancomycin-resistant enterococcus
VIP	vasoactive intestinal peptide
VLDL	very low density lipoproteins

1 Introduction

1 The History of Intestinal Failure and Transplantation

Alan N. Langnas

Major advances in modern medicine often have occurred in giant leaps rather than incrementally; progress in the management of intestinal failure has been no different. The ancient Greeks were the first to propose physiology to explain the workings of the human body. In the traditional Hellenic view, there were three dominant centers of the body: the liver, the heart, and the brain. The liver was thought to be the source of nourishment and growth [1]. This view went virtually unchallenged for 13 centuries. The demonstration of the circulation of blood by William Harvey brought an end to Galenic physiology and the beginnings of our ability to conceptualize a role for intravenous therapies. It was nearly 300 years later that the foundations for organ transplantation were laid down by a French surgeon working in the United States, Alexis Carrel. Dr Carrel effectively demonstrated the ability to anastamose blood vessels and attempt organ transplantation. These exciting discoveries of Sir William Harvey and Nobel Laureate Alexis Carrell provided the inspiration for numerous others and helped usher in the modern era of treatment for intestinal failure.

Early approaches to intestinal failure

Enteral nutritional support

Eating and the digestive process have intrigued mankind for thousands of years. In Hellenic times the only enteral therapies available were alterations in diet or the use of enemas. Interestingly, and not dissimilarly to today, these ancient physicians used enemas in an attempt to improve overall health and treat a variety of other ailments [2,3]. The contents of these rectal infusions included eggs, brandy, wine, milk, and whey and wheat broths [3,4].

Enemas were the only practical method of infusion of nutrition until suitable tools to access the esophagus and stomach were devised. It was not until 1598 that the first description of a hollow tube attached to a bladder filled with food was used to feed directly into the esophagus [3,5]. Improvements on this included the development of a soft, flexible leather tube to provide access to the esophagus and stomach. This was the first time that the idea of an orogastric tube was proposed [3]. John Hunter was an early proponent of enteral feeding and suggested the use of a liquid composed of jellies, milk, water, wine, and eggs [3,6].

The development of parenteral support

The first giant step forward in the evolution of parenteral treatments for intestinal failure was the description of circulation by William (Figure 1.1). Harvey was born in England and studied at Cambridge. In 1600, he traveled to Padua to study anatomy and embryology under Fabricius. On returning to England, he swiftly established his reputation and by 1618 he was selected to be one of the royal physicians [1].

Harvey's challenge was to reconcile his observations from the numerous dissections he carried out with the Galenian description of circulation. Before Harvey's definitive work, the Greek explanation for blood flow stated that blood was created by the liver from chyle and was then drawn into the body by the heart

Intestinal Failure: Diagnosis, Management and Transplantation. Edited by Alan N. Langnas, Olivier Goulet, Eamonn M.M. Quigley and Kelly A. Tappenden.
ISBN 978-1-4051-4637-1.

Figure 1.1 Oil on canvas of Sir William Harvey, artist unknown (1578 to 1657). (Source: http://www.rcplondon.ac.uk.)

in diastole. The new blood was then completely absorbed by the body. The cycle was then repeated with the liver creating new blood [1]. As described by Porter, Harvey's fundamental observation was that blood was forced from the heart in systole and that the amount of blood expelled in an hour by the heart far exceeded the blood volume of the animal. Harvey therefore proposed that the blood must flow in a circuit. His seminal experiment made use of a man's forearm and a tourniquet (Figure 1.2). A ligature was placed around the forearm and tightened to prevent any blood flow to the hand. The ligature was loosened slightly to allow for blood to flow into the hand but tight enough to prevent venous drainage. The hand became swollen and veins engorged. Although capillaries were yet to be discovered, Harvey suggested that a conduit must exist to get blood from the arteries to the veins and, thereby, complete the circuit [1,7].

Following the description of circulation the idea of intravenous infusions was not long in coming. The first reports of this included the intravenous injection of wine and ale in dogs which revealed effects similar to that seen with oral ingestion; later others successfully treated cholera patients with an intravenous infusion of an electrolyte solutions and milk [8,9,13]. The first attempts with fat infusions involved intravenous injections of olive oil in dogs. The dogs died rapidly [10]. By the 1800's physicians began administering fats subcutaneously. There were numerous reports by the end of the 19th century of subcutaneous injections of milk with egg yolk or cod liver oil [10]. Although this represented the first attempts at total parenteral nutrition, the injections were too painful to be practical [11]. It

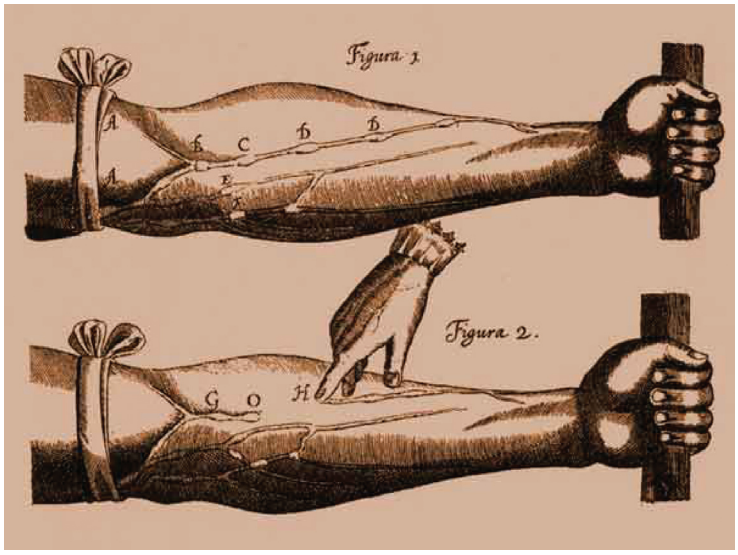

Figure 1.2 Illustration depicting one of Harvey's seminal experiments, which demonstrated that venous blood only travels toward the heart, from *Exercitatio Anatomica de Motu Cordus et Sanguinis in Animalibus,* 1628. (Source: http://www.life.uiuc.edu/ib/494/harvey.html.)

would be another 50 years before a commercial intravenous fat emulsion would be available in the United States.

By the late 1800s the first infusions of glucose and amino acid solutions in man were being reported [10,12,13]. While somewhat successful, the glucose infusions were associated with fever and chills. It was not known that the fevers were due to pyrogens or endotoxin in the solutions. By 1915 a dose response curve for the infusion of glucose was reported and in 1924 the use of continuous glucose infusions were being described [13,14]. The concept that proteins were broken down into amino acids was first described in the late 19th century and subsequently it was determined that polypeptides could be created from amino acids [15]. The first attempts at non-oral protein treatments included proctocylsis enemas and later two Danish scientists reported using intravenous protein infusions, comprised of hydrolyzed beef protein, into goats, and achieved a positive nitrogen balance [10,13,16]. The stage had now been set to usher in the modern era of the treatment of intestinal failure.

The development of modern parenteral nutrition

The development of any new field of study often requires the recognition of a specific medical problem, as well as cause-and-effect relationships. By the early 20th century improvements in anesthesia allowed surgeons to tackle more complex operations. As noted by Arvid Wretlind in a comprehensive review of this topic, postoperative complications compelled surgeons to examine a variety of factors including comorbidities such as the nutritional status of the patient. One of the first reports of a potential link between nutritional status and surgical outcomes was published in 1936 by Studley. He observed that patients with chronic peptic ulcer disease who had lost more than 20% of their weight before surgery died at a much greater rate when compared to patients who had lost less than 20% of their weight [17]. The origins of surgical nutrition became a strong impetus to take this bedside problem to the laboratory.

Another big step forward in the development of modern intravenous nutrition was made by Dr Robert Elman. Dr Elman was a surgeon practicing in St Louis whose specialty was the open treatment of burns. Although before Dr Elman there had been reports of successful intravenous infusions of amino acids in goats, his seminal contribution was the demonstration that amino acids could be effectively and safely administered intravenously to humans [13,16,18]. The amino acid solutions were prepared as an enzymatic hydrolysate of casein and pancreas. This product was soon known as Amigen. As noted by Wretland, there were still concerns that intravenous amino acids would not be metabolized by the liver and could result in end-organ injuries, particularly to the brain [10]. Further experiments eventually demonstrated that the utilization of intravenous enzymatic casein hydrolysate was the same regardless of route of administration, whether intravenous or intraportal [19].

With the recognition that amino acid infusions were both relatively safe and effective, limits to its use were being noted. It was noted that the protein hydrolysates contained only 50% free amino acids, resulting in the delivery of only about 2 kcal/gram. This eventually led to the development of crystalline amino acids. Bansi was the first to introduce a crystalline L-amino acid solution in 1964 [20]. Numerous improvements took place, including the ability to manipulate the amino acid patterns in various products. Soon, limits to the effectiveness of parenteral nutrition were observed, including the development of essential fatty acid deficiencies. First, in order to provide adequate calories, the volume of administered fluids often exceeded 3 liters per day. This large amount of fluid was difficult for many patients to manage and diuretics were typically required. Second, attempts at administering high glucose concentration infusions (>10%) via peripheral veins resulted in thrombophlebitis. Central venous access was not yet routinely performed, and clinicians looked for other sources of parenteral calories. Intravenous alcohol was tried because of the relatively high caloric density (7 kcal/gm). While alcohol was a good source of energy, the side effects of the infusion prevented it from practical consideration. The next best candidate for increasing calories was the administration of fats. The infusion of fats also would prevent the development of fatty acid deficiencies and its clinical manifestations such as a skin rash.

Interest in developing a form of fat for intravenous infusion had been going on since the early 20th century. The first attempts at fat infusions in children

occurred in the 1920s. The major limit to supplying this high caloric source was the need for an emulsifying agent. Cotton seed products became available in the 1950s, but side effects, including nausea, vomiting, fevers, rash, and liver dysfunction, limited its application [10]. The Food and Drug Administration (FDA) eventually stopped its use in 1964. In 1961, a Swedish scientist, Arvid Wretlind, found a relatively nontoxic formulation, soon to be known as Intralipid. The key to his success was combination of soy bean oil emulsified by egg yolk phospholipids in glycerol [10].

By 1968, all of the pieces were in place for Dr. Dudrick and coworkers at the University of Pennsylvania to demonstrate growth and development in beagle puppies with intravenous nutrition [21]. The beagle puppies were fed through an intravenous catheter placed in to the superior vena cava via the external jugular vein. Isocaloric oral calories were given to the littermate controls. The beagles that were fed entirely intravenously actually surpassed the controls in terms of weight gain and were equal in skeletal growth and activity level. This experimental work was the culmination of many years of clinical activity and leadership by Jonathan Rhoads in the Department of Surgery.

One major hurdle still persisted: safe access to the central venous circulation. Rhoads and colleagues at the University of Pennsylvania were using the "5 liter program" to provide adequate calories through a peripheral vein [22]. This approach required close monitoring of the patient and frequent use of diuretics. If patients could receive higher concentrations of glucose via a central vein, then these large volumes of fluid could be avoided. This group had begun placing catheters in the central venous system via the antecubital route in terminally ill cancer patients. At autopsy, numerous clots were noted along the catheter and a fear of pulmonary emboli limited its use [22]. In a first person account of these events Dudrick notes that a 1967 report of percutaneous infraclavicular venepuncture of the subclavian vein for the purpose of central venous pressure monitoring encouraged surgeons at the University of Pennsylvania to use this approach for the placement of a central venous catheter to administer parenteral nutrition [22,23]. It would now be possible and practical to provide long-term parenteral nutrition. Dudrick writes that in 1967, he was asked to consult on an unfortunate little girl born with intestinal atresia [22]. The child was destined to die by starvation. She weighed about 2 kg at the initiation of total parenteral nutrition. Over the ensuing 22 months of her life, she was able achieve growth, development, and a maximum weight of 8.3 kg [24]. The modern era of parenteral nutrition had begun.

The development of modern enteral nutrition

In parallel with the above described progress in parenteral nutrition came developments in enteral nutrition. As described in the comprehensive review by Chernoff, early attempts involved the placement of a weighted nasal-jejunal tube, but many physicians were not convinced that predigested protein hydroysates could be administered safely to humans. By the 1930s, it was accepted that these protein solutions could be fed to surgical patients [25]. Skim milk treated with acid, pepsin, and some vitamins was a common recipe [5]. Further advances led to the development of an infant formula that could be used for babies with allergies and other nonspecific gastrointestinal ailments. In 1943, Mulholland and coworkers demonstrated the benefits of enteral versus parenteral nutrition in the convalescing postoperative patient [3,26]. Soon thereafter, jejeunostomy feeding tubes were being placed at the time of surgery and the first enteral feeding pumps were in use.

Various enteral recipes were developed to create food that was well tolerated and provided the requisite balance of calories, nutrients, and vitamins. Many of these blenderized formulas were made in hospital kitchens [3]. One major advance came directly from the emerging programs at the National Aeronautics and Space Administration (NASA). Nutritionists were asked to develop a diet for astronauts with the central prerequisite being the production of a low fecal output. Elemental diets were a direct consequence of these efforts, although the astronauts were very critical regarding their taste [5,27]. Continued developments in enteral formulas over the past 20 years have resulted in the evolution of feeds for very specific clinical conditions, including renal, live, and pulmonary failure. Advances in enteral nutrition have been less dramatic than those seen with parenteral nutrition,

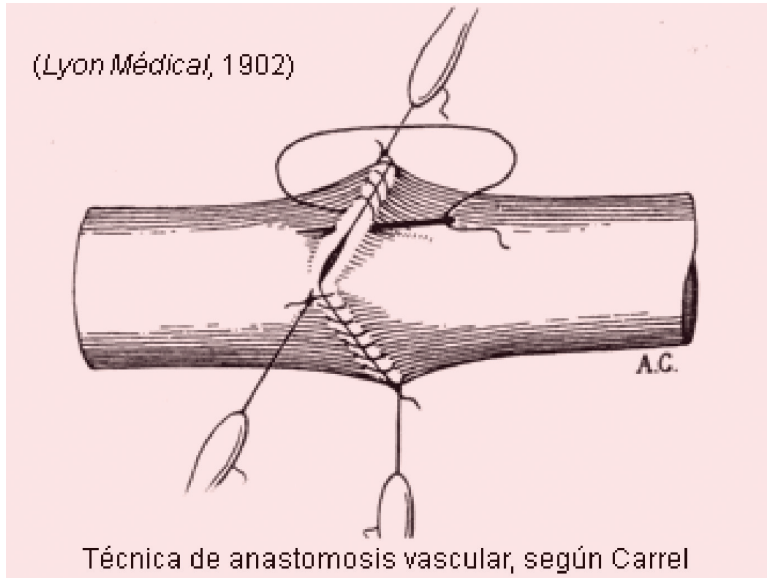

Figure 1.3 A drawing by Carrel, demonstrating a new technique for anastamosis blood vessel together.

but enteral nutrition remains cheaper, safer, and often more effective.

History of intestinal transplantation

The ancient beginnings of transplantation are represented in Greek mythology by the Chimera. Homer first describes the Chimera in the *Iliad* as a "thing of immortal make, not human, lion fronted and snake behind, goat in the middle" [28]. Today, the Chimera is used to describe objects that have the attributes of more than one source, often in the context of organ transplantation. The development of intestinal transplantation paralleled the development of other types of organ transplantation. The seemingly hopeless outcome of early attempts at intestinal transplantation needs to be seen in the context of an era where total parenteral nutrition had yet to be developed and all of these unfortunate patients were going to starve to death. The success that we see with intestinal transplantation today is based on progress in two interrelated areas, surgery and immunology.

The key to the development of solid organ transplantation was the ability to successfully and reliably restore blood flow to the transplanted organ by suturing donor and recipient blood vessels together. As noted by Sade in a paper describing Alexis Carrel, conventional surgical thinking in the late 1800's was that blood vessels could only be ligated not repaired [29]. A medical student at the University of Lyon, Alexis Carrel, challenged that surgical dogma; if other human tissue could be sewn back together why not blood vessels [29]? Carrel published his first articles on vacular anastamosis at that time [30,31] Figure 1.3. Disillusioned with his prospects in France, Carrel left Lyon in 1904 for the University of Chicago and, eventually, the Rockefeller Institute in New York where he continued his research. In the United States, he perfected the surgical technique by using finer sutures and developed the triangulation technique for anatamosing small blood vessels. His ability to anastamose blood vessels led him to attempt a variety of organ transplants in dogs, including that of the intestine [32]. By 1930 Carrel was developing a machine to preserve organs for transplantation and collaborated with the famous aviator Charles Lindberg. Working together for over 5 years they attempted to construct a device to perfuse and oxygenate organs [29,33]. Carrel was known as an innovative surgeon that placed a great deal of emphasis on intuition including the quote, "All great men are gifted with intuition. They know without reasoning of analysis what they need to know." Later in life he accepted a more controversial role in the French

Figure 1.4 Photograph of the first successful kidney transplant team. Front row (left to right): Richard Herrick, kidney transplant recipient; Ronald Herrick, kidney donor. Back row (left to right): The Brigham transplant team: Dr Joseph E. Murray, surgeon for the recipient; Dr John P. Merrill, nephrologist and coleader of the team; and Dr J. Hartwell Harrison, urological surgeon for the donor. (Source: http://www.donatelife.org/transplant/murray.html.)

Vichy government after the Genman invasion of World War II. Carrel received the Nobel Prize for Physiology and Medicine in 1912 for his work in both vascular anastamosis and organ transplantation.

While Carrel seemingly overcame the technical limits of organ transplantation, the biology of organ transplantation was not known. At the beginning of World War II, many British pilots were being severely burned. The Brazilian-born British zoologist Peter Medawar was asked by the British government to determine why skin grafts taken from one individual would not graft permanently graft to another. Working with the plastic surgeon Thomas Gibson, they developed and studied a rabbit model of skin grafting. Their findings were the first to suggest that it was the immune system that was responsible for the destruction of the skin allograft [34]. Medawar received the Nobel Prize for Physiology and Medicine, in 1960, for this work. Finally, in 1954, Murray and coworkers, understanding the surgical and biologic basis of transplantation, became the first to perform a successful kidney transplant between identical twins [35].

The technical foundations to intestinal transplantation can be linked to professors Lillehi and Starzl. At the University of Minnesota, Lillehei performed autotransplants and homotransplants of the intestine in dogs. These operations demonstrated many things including that the intestine could tolerate preservation outside the dog's body and would then function adequately following re-implantation [36,37]. Starzl later, reported the startling technical feat of transplanting what would be referred to today as a multivisceral transplant in dogs [36,38]. The early successes with kidney, liver, and heart transplants, combined with the fact that long-term parenteral nutrition would not be available until the mid-1970s, provided the impetus to surgeons to attempt the first human intestinal transplants. Over the next 25 years, numerous intestinal transplants were performed, but there were no survivors [36]. In 1987, using cyclosporine-based