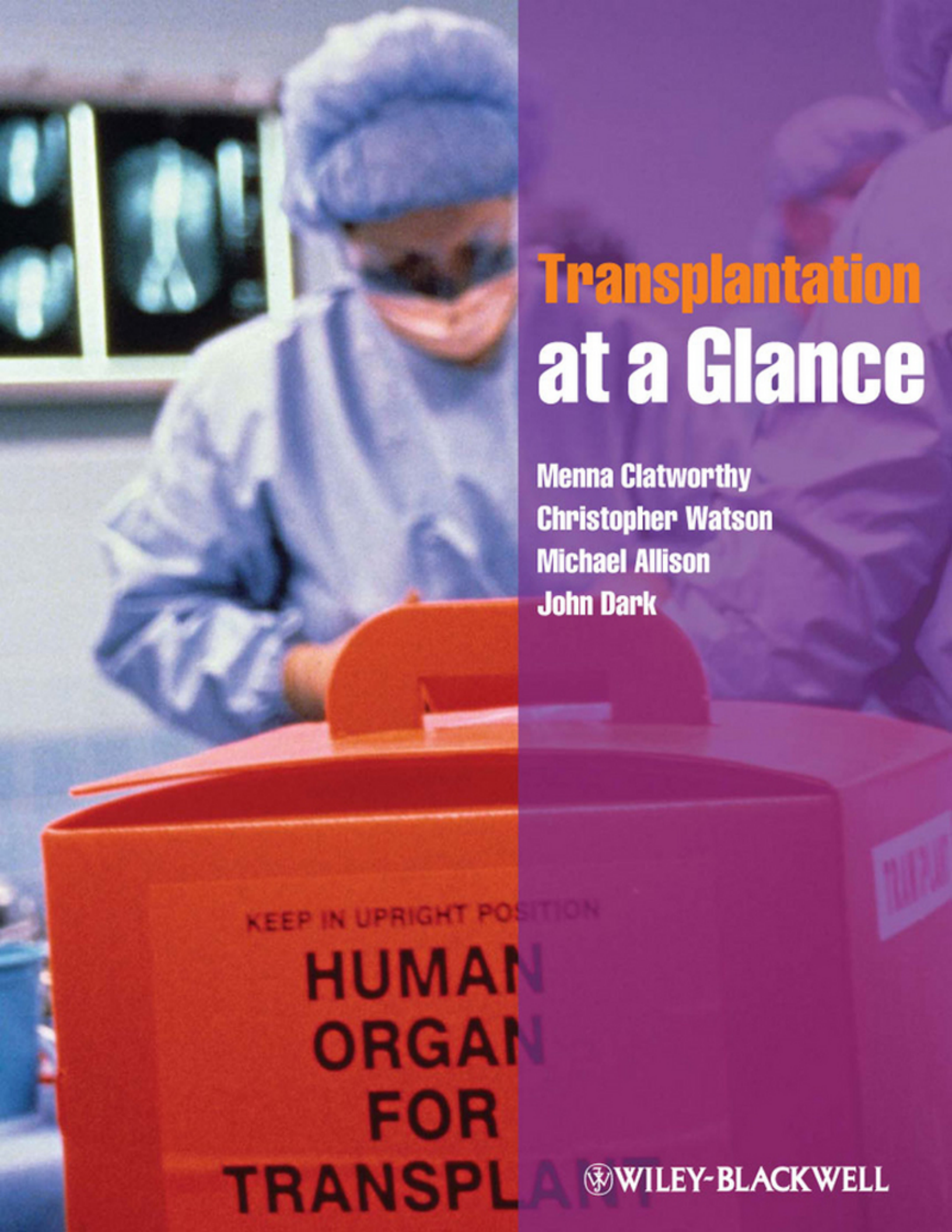

Transplantation at a Glance

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Preface

The early attempts at transplantation in the first half of the 20th century were limited by technical challenges and ignorance of the immune response. Half a century later, with an appreciation of some aspects of human immunology, the first successful renal transplant was performed between identical twins. From these beginnings transplantation has progressed from being an experimental treatment available to a few, to a thriving discipline providing life-changing treatment for many. Its power to dramatically transform the quality and quantity of life continues to capture and inspire those involved at all levels of care. Transplantation is a truly multidisciplinary specialty where input from physicians, surgeons, tissue-typists, nurses, coordinators and many others is required in the provision of optimal care. It is also a rapidly moving discipline in which advances in surgical technique and immunological knowledge are constantly being used to improve outcomes. As a newcomer to the field, the breadth of knowledge required can appear bewildering, and it is with this in mind that we have written *Transplantation at a Glance*. We hope that in this short, illustrated text we have provided the reader with a succinct, yet comprehensive overview of the most important aspects of transplantation. The book is designed to be easily read and to rapidly illuminate this exciting subject. We have long felt that many aspects of transplantation are best conveyed by diagrammatic or pictorial representation, and it was this conviction that led to the creation of *Transplantation at a Glance*. In particular, the two fundamentals of transplantation, basic immunology and surgical technique, are best learned through pictures. For those approaching transplantation without a significant background in

immunology or the manifestations of organ failure, we have provided an up-to-date, crash course that allows the understanding of concepts important in transplantation so that subsequent chapters can be easily mastered. For those without a surgical background, the essential operative principles are simply summarised. Most importantly, throughout the text we have aimed to provide a practical and clinically relevant guide to transplantation which we hope will assist those wishing to rapidly familiarise themselves with the field, regardless of background knowledge.

MRC
CJEW

List of Abbreviations

6-MP	6-mercaptopurine
ACR	acute cellular rejection; albumin–creatinine ratio
ADCC	antibody-dependent cellular cytotoxicity
ADH	antidiuretic hormone
AKI	acute kidney injury
ALD	alcohol-related liver disease
ALG	anti-lymphocyte globulin
ALP	alkaline phosphatase
ALT	alanine transaminase
AMR	antibody-mediated rejection
ANCA	antineutrophil cytoplasmic antibody
APC	antigen-presenting cell
APD	automated peritoneal dialysis
APKD	adult polycystic kidney disease
ARB	angiotensin receptor blocker
AST	aspartate transaminase
ATG	anti-thymocyte globulin
ATN	acute tubular necrosis
AV	atrioventricular
AVF	arteriovenous fistula
BAL	bronchoalveolar lavage
BCR	B cell receptor
BMI	body mass index
BOS	bronchiolitis obliterans syndrome

BP	blood pressure
CABG	coronary artery bypass graft
CAPD	continuous ambulatory peritoneal dialysis
CAV	cardiac allograft vasculopathy
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
CDR	complementarity-determining region
CF	cystic fibrosis
CKD	chronic kidney disease
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CO	carbon monoxide; cardiac output
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise testing
CPP	cerebral perfusion pressure
cRF	calculated reaction frequency
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
CTA	composite tissue allotransplantation
CXR	chest X-ray
DAMP	danger/damage-associated molecular pattern
DBD	donation after brain death
DC	dendritic cell
DCD	donation after circulatory death
DGF	delayed graft function
DLCO	diffusing capacity of the lung for carbon monoxide
DSA	donor-specific antibodies

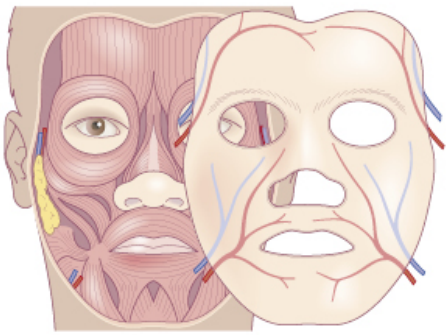
DTT	dithiothreitol
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECMO	extra-corporeal membrane oxygenator
EEG	electroencephalogram
ELISA	enzyme-linked immunosorbent assay
EPO	erythropoietin
EPS	encapsulating peritoneal sclerosis
ERCP	endoscopic retrograde cholangio-pancreatography
ESRF	end-stage renal failure
EVLP	ex vivo lung perfusion
FcγR	Fc-gamma receptor
FEV_1	forced expiratory volume in 1 second
FFP	fresh frozen plasma
FGF	fibroblast growth factor
FP	fusion protein
FSGS	focal segmental glomerulosclerosis
FVC	forced vital capacity
GDM	gestational diabetes mellitus
GERD	gastro-oesophageal reflux disease
GFR	glomerular filtration rate
GN	glomerulonephritis
HAI	healthcare-associated infection
HAS	human albumin solution
HBIG	hepatitis B immune globulin
HBV	hepatitis B virus
HCV	hepatitis C virus

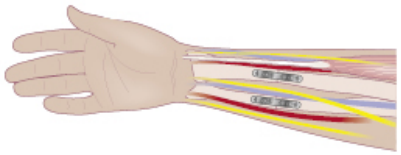
HD	haemodialysis
HLA	human leucocyte antigen
HSP	heat shock protein
HSV	herpes simplex virus
IAK	islet after kidney
ICP	intracranial pressure
IF	interstitial fibrosis
IFALD	intestinal failure-associated liver disease
IFN	interferon
IL	interleukin
IMPDH	inosine monophosphate dehydrogenase
IMV	inferior mesenteric vein
INR	international normalised ratio
IPF	idiopathic pulmonary fibrosis
ITA	islet transplantation alone
ITU	intensive therapy unit
IVC	inferior vena cava
JVP	jugular venous pressure
KIR	killer-cell immunoglobulin-like receptor
KS	Kaposi’s sarcoma
LV	left ventricular
LVAD	left ventricular assist device
LVEDP	left ventricular end diastolic pressure
LVH	left ventricular hypertrophy
mAb	monoclonal antibody
MAC	membrane attack complex
MAP	mean arterial pressure

MELD	model for end-stage liver disease
MHC	major histocompatibility complex
MI	myocardial infarction
MMF	mycophenolate mofetil
MODY	maturity onset diabetes of the young
MPA	mycophenolic acid
MPAP	mean pulmonary arterial pressure
MPS	mycophenolate sodium
MR	magnetic resonance
MRSA	methicillin-resistant *Staphylococcus aureus*
NAFLD	non-alcoholic fatty liver disease
NK	natural killer
NODAT	new onset diabetes after transplant
NSAID	non-steroidal anti-inflammatory drug
ODR	organ donor register
PA	pulmonary artery
PAK	pancreas after kidney
PAMP	pathogen-associated molecular pattern
PCR	polymerase chain reaction; protein–creatinine ratio
PD	peritoneal dialysis
PN	parenteral nutrition
PRA	panel reactive antibodies
PTA	pancreas transplant alone
PTC	peritubular capillary
PTH	parathyroid hormone
PTLD	post-transplant lymphoproliferative disease
PVD	peripheral vascular disease

PVR	pulmonary vascular resistance
RFA	radiofrequency ablation
RRT	renal replacement therapy
SAP	serum amyloid protein
SMA	superior mesenteric artery
SMV	superior mesenteric vein
SPK	simultaneous pancreas and kidney
T3	triiodothyronine
TA	tubular atrophy
TACE	trans-arterial chemo-embolisation
TCR	T cell receptor
TGF	transforming growth factor
TIA	transient ischaemic attack
TIN	tubulointerstitial nephritis
TLR	toll-like receptor
TMR	T cell-mediated rejection
TNF	tumour necrosis factor
TPG	transpulmonary pressure gradient
TPMT	thiopurine S-methyltransferase
TPR	total peripheral resistance
US	ultrasound
VAD	ventricular assist device
VRE	vancomycin-resistant enterococci
VZV	varicella zoster virus

1
History of Transplantation





2005: Devauchelle & Dubernard perform the first face transplant

1998: Dubernard performs the first hand transplant

1990s: Tacrolimus, sirolimus and mycophenolate immunosuppressants introduced

1988: Grant & Wall perform successful first liver and small bowel transplant

1987: Reitz performs the first heart-lung transplant in Stanford, using ciclosporin

1978: Calne first uses ciclosporin in clinic

1971: Collins first uses kidney cold storage solution

1968: UK's first heart and liver transplants

1966: Lillehei performs first successful pancreas transplant

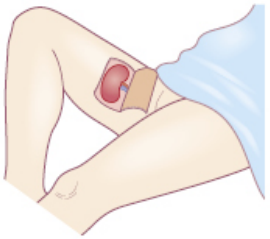
1960: UK's first kidney transplant (Woodruff)

1960: Calne & Murray use azathioprine as first chemical immunosuppressant in Boston

1951: Boston & Parisian surgeons perform kidney transplants from live donors (and two from Madame Guillotine)

1943: Wilhelm Kolff makes first dialysis machine

1936: Voronoy performs first human kidney transplant – into the thigh



1906: Jaboulay transplants animal kidneys into the antecubital fossa of two patients

2000

1990

1980

1970

1960

1950

1940

1930

1920

1910

1900

1988: Winter & Waldmann produce Campath 1H (alemtuzumab), the first humanised monoclonal antibody

1988: OKT3 (muromonab-CD3) – first monoclonal antibody licensed in transplantation

1975: Kohler & Milstein discover technique to make monoclonal antibodies

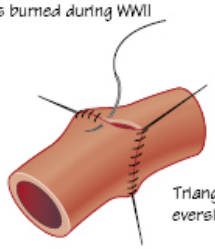
1968: Cooley performs first heart-lung transplant

1967: Barnard performs first heart transplant following Shumway's pioneering research

1963: Tom Starzl performs first liver transplant, though success not achieved until 1967

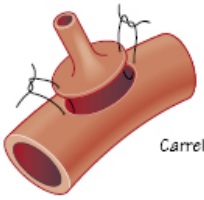
1954: Joe Murray performs first successful kidney transplant between identical twins

1945: Medawar describes acute rejection of skin grafts in pilots burned during WWII



Triangulation and eversion of the edges

1912: Carrel awarded Nobel Prize for techniques of vascular anastomosis



Carrel patch

Fundamentals

Vascular Anastomoses

Transplantation of any organ demands the ability to join blood vessels together without clot formation. Early attempts inverted the edges of the vessels, as is done in bowel surgery, and thrombosis was common. It wasn't until the work of Jaboulay and Carrel that eversion of the edges was shown to overcome the early thrombotic problems, work that earned Alexis Carrel the Nobel Prize in 1912. Carrel also described two other techniques that are employed today, namely triangulation to avoid narrowing an anastomosis and the use of a patch of neighbouring vessel wall as a flange to facilitate sewing, now known as a Carrel patch.

Source of Organs

Having established how to perform the operation, the next step to advance transplantation was to find suitable organs. It was in the field of renal transplantation that progress was made, albeit slowly. In Vienna in 1902, Ulrich performed an experimental kidney transplant between dogs, and four years later in 1906, Jaboulay anastomosed animal kidneys to the brachial artery in the antecubital fossa of two patients with renal failure.

Clinical transplantation was attempted during the first half of the 20th century, but was restricted by an ignorance of the importance of minimising ischaemia – some of the early attempts used kidneys from cadavers several hours, and occasionally days, after death. It wasn't until the mid-1950s that surgeons used 'fresh' organs, either from live patients who were having kidneys removed for transplantation or other reasons, or in Paris, from recently guillotined prisoners.

Where to Place the Kidney

Voronoy, a Russian surgeon in Kiev, is credited with the first human-to-human kidney transplant in 1936. He transplanted patients who had renal failure due to ingestion of mercuric chloride; the transplants never worked, in part because of the lengthy warm ischaemia of the kidneys (hours). Voronoy transplanted kidneys into the thigh, attracted by the easy exposure of the femoral vessels to which the renal vessels could be anastomosed. Hume, working in Boston in the early 1950s, also transplanted kidneys into the thigh, with the ureter opening on to the skin to allow ready observation of renal function. It was René Küss in Paris who, in 1951, placed the kidney intra-abdominally into the iliac fossa and established the technique used today for transplanting the kidney.

Early Transplants

The 1950s was the decade that saw kidney transplantation become a reality. The alternative, dialysis, was still in its infancy so the reward for a successful transplant was enormous. Pioneers in the US and Europe, principally in Boston and Paris, vied to perform the first long-term successful transplant, but although initial function was now being achieved with ‘fresh’ kidneys, they rarely lasted more than a few weeks. Carrel in 1914 recognised that the immune system, the ‘reaction of an organism against the foreign tissue’, was the only hurdle left to be surmounted. The breakthrough in clinical transplantation came in December 1954, when a team in Boston led by Joseph Murray performed a transplant between identical twins, so bypassing the immune system completely and demonstrating that long-term survival was possible. The kidney recipient, Richard Herrick, survived 8 years following the transplant, dying from recurrent disease; his

twin brother Ronald died in 2011, 56 years later. This success was followed by more identical-twin transplants, with Woodruff performing the first in the UK in Edinburgh in 1960.

Development of Immunosuppression

Demonstration that good outcomes following kidney transplantation were achievable led to exploration of ways to enable transplants between non-identical individuals. Early efforts focused on total body irradiation, but the side effects were severe and long-term results poor. The anticancer drug 6-mercaptopurine (6-MP) was shown by Calne to be immunosuppressive in dogs, but its toxicity led to the evaluation of its derivative, azathioprine. Azathioprine was used in clinical kidney transplantation in 1960 and, in combination with prednisolone, became the mainstay of immunosuppression until the 1980s, when ciclosporin was introduced. It was Roy Calne who was also responsible for the introduction of ciclosporin into clinical transplantation, the drug having originally been developed as an antifungal drug, but shelved by Sandoz, the pharmaceutical company involved, as ineffective. Jean Borel, working for Sandoz, had shown it to permit skin transplantation between mice, but Sandoz could foresee no use for such an agent. Calne confirmed the immunosuppressive properties of the drug in rodents, dogs and then humans. With ciclosporin, clinical transplantation was transformed. For the first time a powerful immunosuppressant with limited toxicity was available, and a drug that permitted successful non-renal transplantation.

Non-Renal Organ Transplants

Transplantation of non-renal organs is an order of magnitude more difficult than transplantation of the kidney; for liver, heart or lungs the patient's own organs must first be removed before the new organs are transplanted; in kidney transplantation the native kidneys are usually left in situ.

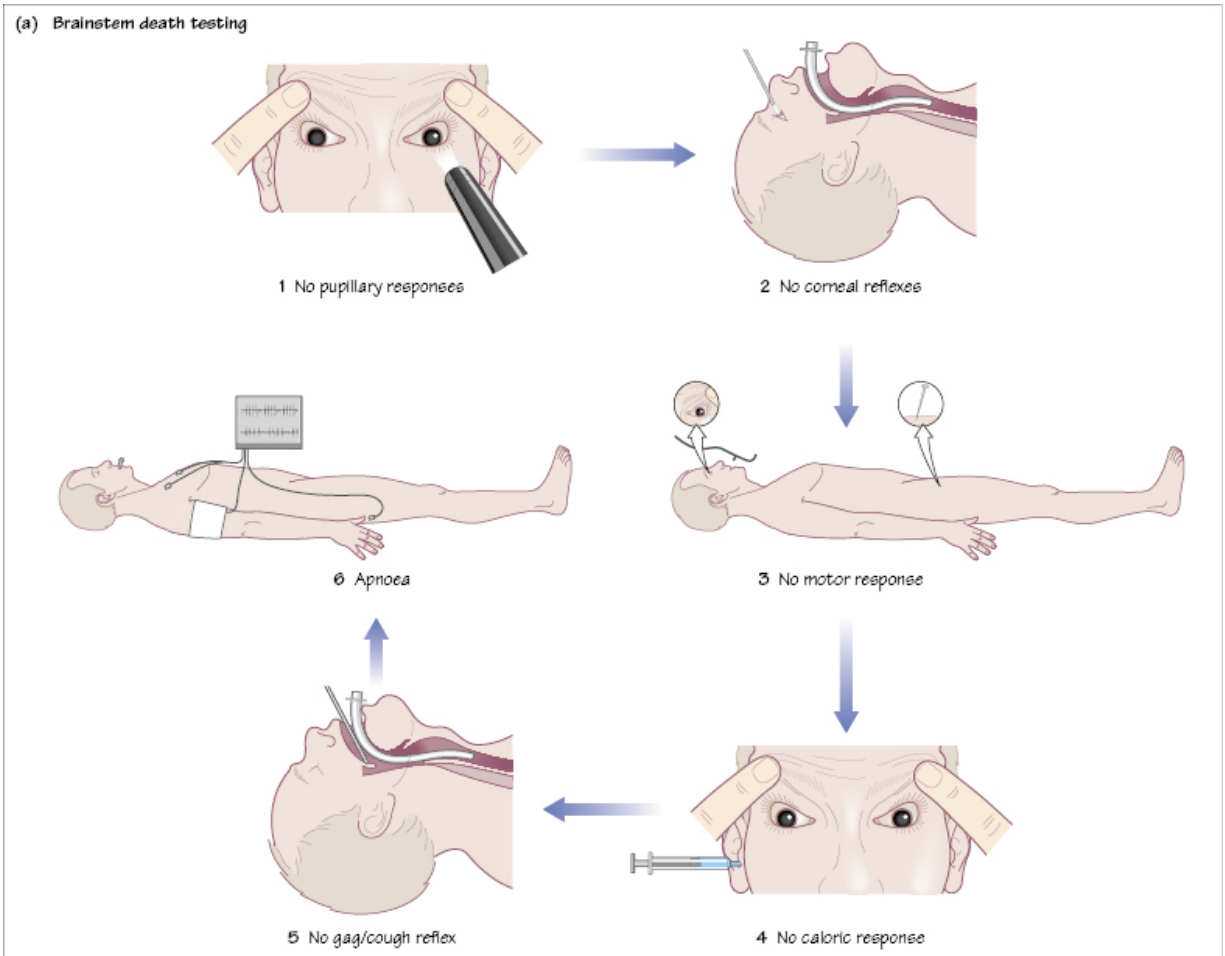
After much pioneering experimental work by Norman Shumway to establish the operative technique, it was Christiaan Barnard who performed the first heart transplant in 1967 in South Africa. The following year the first heart was transplanted in the UK by Donald Ross, also a South African; and 1968 also saw Denton Cooley perform the first heart-lung transplant.

The first human liver transplantation was performed by Tom Starzl in Denver in 1963, the culmination of much experimental work. Roy Calne performed the first liver transplant in the UK, something that was lost in the press at the time, since Ross's heart transplant was carried out on the same day.

Although short-term survival (days) was shown to be possible, it was not until the advent of ciclosporin that clinical heart, lung and liver transplantation became a realistic therapeutic option. The immunosuppressive requirements of intestinal transplants are an order of magnitude greater, and their success had to await the advent of tacrolimus.

In addition, it should be remembered that at the time the pioneers were operating there were no brainstem criteria for the diagnosis of death, and the circulation had stopped some time before the organs were removed for transplantation.

2
Diagnosis of Death and Its Physiology



Cerebral perfusion pressure (CPP) =
mean arterial pressure (MAP) − intracranial pressure (ICP)

Stages in the Cushing reflex

1. From the above equation, as ICP rises CPP falls
2. Baroreceptors in the brainstem detect falling CPP, triggering the sympathetic nervous system, which causes vasoconstriction: MAP and heart rate rise
   Further rise in ICP triggers parasympathetic activity, slowing the heart rate
3. As ICP rises further coning occurs, where the brainstem herniates through the foramen magnum. Catecholamine levels peak 20x to 80x higher than normal; systolic BP may peak over 300 mmHg
4. Post coning the BP falls. Neuroendocrine changes occur as hypothalamic pituitary axis falls

Diagnosing Death

Circulatory Death

Traditionally, death has been certified by the absence of a circulation, usually taken as the point at which the heart stops beating. In the UK, current guidance suggests that death may be confirmed after 5 minutes of observation following cessation of cardiac function (e.g. absence of heart sounds, absence of palpable central pulse or asystole on a continuous electrocardiogram). Organ donation after circulatory death (DCD) may occur following confirmation that death has occurred (also called non-heart-beating donation).

There are two sorts of DCD donation, controlled and uncontrolled.

Controlled DCD donation occurs when life-sustaining treatment is withdrawn on an intensive therapy unit (ITU). This usually involves discontinuing inotropes and other medicines, and stopping ventilation. This is done with the transplant team ready in the operating theatre able to proceed with organ retrieval as soon as death is confirmed.

Uncontrolled DCD donation occurs when a patient is brought into hospital and, in spite of attempts at resuscitation, dies. Since such events are unpredictable a surgical team is seldom present or prepared, and longer periods of warm ischaemia occur (see later).

Brainstem Death

Brainstem death (often termed simply brain death) evolved not for the purposes of transplantation, but following technological advances in the 1960s and 1970s that enabled patients to be supported for long periods on a ventilator while deep in coma. There was a requirement to

diagnose death in such patients whose cardiorespiratory function was supported artificially. Before brainstem death can be diagnosed, five pre-requisites must be met.

Pre-Requisites Before Brainstem Death Testing Can Occur

1 The patient's condition should be due to irreversible brain damage of known aetiology.

2 There should be no evidence that the comatose state is due to depressant drugs – drug levels should be measured if doubt exists.

3 Hypothermia as a cause of coma has been excluded – the temperature should be >34°C before testing.

4 Potentially reversible circulatory, metabolic and endocrine causes have been excluded. The commonest confounding problem is hypernatraemia, which develops as a consequence of diabetes insipidus, itself induced by failure of hypothalamic antidiuretic hormone (ADH) production.

5 Potentially reversible causes of apnoea have been excluded, such as neuromuscular blocking drugs or cervical cord injury.

Tests of Brainstem Function

1 Pupils are fixed and unresponsive to sharp changes in the intensity of incident light.

2 The corneal reflex is absent.

3 There is no motor response within the cranial nerve distribution to adequate stimulation of any somatic area, such as elicited by supra-orbital pressure.

4 The oculo-vestibular reflexes are absent: at least 50 ml of ice-cold water is injected into each external auditory meatus. In life, the gaze moves to the side of injection; in death, there is no movement.

5 There is no cough reflex to bronchial stimulation, e.g. to a suction catheter passed down the trachea to the carina, or gag response to stimulation of the posterior pharynx with a spatula.

6 The apnoea test: following pre-oxygenation with 100% oxygen, the respiratory rate is lowered until the pCO_2 rises above 6.0 kPa (with a pH less than 7.4). The patient is then disconnected from the ventilator and observed for 5 minutes for a respiratory response.

Following brainstem death spinal reflexes may still be intact, resulting in movements of the limbs and torso.

These criteria are used in the UK; different criteria exist elsewhere in the world, some countries requiring an unresponsive electroencephalogram (EEG) or demonstration of no flow in the cerebral arteries on angiography. The UK criteria assess brainstem function without which independent life is not possible.

Causes of Death

Most organ donors have died from an intracranial catastrophe of some sort, be it haemorrhage, thrombosis, hypoxia, trauma or tumour. The past decade has seen a change in the types of brain injury suffered by deceased organ donors; deaths due to trauma are much less common, and have been replaced by an increased prevalence of deaths from stroke. This is also a reflection of the increased age of organ donors today.

Physiology of Brainstem Death

Cushing’s Reflex and the Catecholamine Storm

Because the skull is a rigid container of fixed volume, the swelling that follows a brain injury results in increased intracranial pressure (ICP). The perfusion pressure of the brain is the mean arterial pressure (MAP) minus the ICP, hence as ICP rises, MAP must rise to maintain perfusion. This is triggered by baroreceptors in the brainstem that activate the autonomic nervous system, resulting in catecholamine release. Catecholamine levels may reach 20-fold those of normal, with systemic blood pressure rising dramatically.

The ‘catecholamine storm’ has deleterious effects on other organs: the left ventricle is placed under significant strain with subendocardial haemorrhage, and subintimal haemorrhage occur in arteries, particularly at the points of bifurcation, predisposing to thrombosis of the organ following transplantation; perfusion of the abdominal organs suffers in response to the high catecholamine levels. Eventually the swollen brain forces the brainstem to herniate down through the foramen magnum (coning), an occurrence that is marked by its compression of the oculomotor nerve and resultant pupillary dilatation. Once coning has occurred circulatory collapse follows with hypotension, secondary myocardial depression and vasodilatation, with failure of hormonal and neural regulators of vascular tone.

Decompressive Craniectomy

Modern neurosurgical practices include craniectomy (removal of parts of the skull) to allow the injured brain to swell, reducing ICP and so maintaining cerebral perfusion. While such practices may protect the brainstem, the

catastrophic nature of the brain injury may be such that recovery will not occur and prolongation of treatment will be inappropriate. Such is the setting in which DCD donation often takes place.

Neuroendocrine Changes Associated with Brain Death

Following brainstem death a number of neuroendocrine changes occur, most notably the cessation of ADH secretion, resulting in diabetes insipidus and consequent hypernatraemia. This is treated by the administration of exogenous ADH and 5% dextrose. Other components of the hypothalamic-pituitary axis may also merit treatment to optimise the organs, including the administration of glucocorticoids and triiodothyronine (T3).