EDITED BY TOBY L. SIMON • ERIC A. GEHRIE
JEFFREY McCULLOUGH • JOHN D. ROBACK • EDWARD L. SNYDER

ROSSI'S PRINCIPLES OF TRANSFUSION MEDICINE

SIXTH EDITION

WILEY Blackwell

Rossi's Principles of Transfusion Medicine

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Preface

In 1983, the National Heart, Lung and Blood Institute (NHLBI) awarded five medical school faculty the first of what were to be a host of Transfusion Medicine Academic Awards. The purpose of the program was to enhance instruction in and exposure to the essential principles related to transfusion of blood into patients. This was considered a neglected area in medical education. Embedded in that decision was the idea that blood banking was part of a broader medical field now termed transfusion medicine.

Dr. Ennio C. Rossi was one of these first five awardees. At that time, he was a professor at Northwestern University School of Medicine in Chicago and director of its apheresis unit. Dr. Rossi was approached by Williams and Wilkins to put together a major textbook in this newly identified field of transfusion medicine. Dr. Rossi subsequently recruited two coeditors: Dr. Toby Simon, a board certified transfusion medicine physician who was also one of the first five NHLBI awardees, and Dr. Gerald Moss, a prominent surgeon who had notable research achievements in oxygen transport. Thus, the first edition of Principles of Transfusion Medicine was launched by two hematologists and a surgeon. After the second edition, Dr. Rossi retired and Dr. Toby Simon assumed the senior editor role. It was decided to add Dr. Rossi's name to the title in recognition of his conception of the role of the book and to establish continuity for subsequent editions. Sadly, Dr. Rossi passed away on September 3, 2021. We dedicate this book to his memory and quote as follows from the first two paragraphs of the Preface to the first edition published in 1991:

> Blood transfusion is an essential part of medical care and indispensable for the support of increasingly more sophisticated surgery. In the past, transfusion decisions were simple because therapeutic options were few. Now, decisions are more complicated. Transplantation biology and immunohematology are tightly intertwined, and transplantation surgery is frequently contingent upon special transfusion support. Advances in the technology of plasma fractionation and apheresis now provide a broad array of services for a large variety of clinical problems. Balanced against these benefits are the risks of blood-transmitted diseases, which have been underscored in the public consciousness by the emergence of acquired immunodeficiency syndrome (AIDS). Autologous transfusion and products of genetic engineering, such as hematopoietic growth factors, are being made available to diminish the risk, albeit small, of transfusion-transmitted disease by homologous blood. As these and other innovations render transfusion therapy more complex, blood banking has developed a clinical arm, transfusion medicine, to deal with these complexities.
>
> *Principles of Transfusion Medicine* will attempt to define the proper use of blood in clinical care. It is intended for the clinicians who prescribe blood, for the students who expect to enter clinical practice, for the scientists, physicians, nurses, technologists, and others who ensure the quality of our blood services. Many diverse sciences are applied to the preparation of blood for transfusion, and virtually all medical and surgical specialties must employ transfusion, from time to time, in care of their patients. For this reason, transfusion medicine is, of necessity, multidisciplinary.

In preparation of this sixth edition, we have also been challenged by a pandemic. In response to this pandemic, two chapters in the early part of the book have been added, detailing how our specialty responded to the emergency and the lessons learned. In addition, we have chapters focusing on other "megatrends": the application of molecular biology to the basics of matching donor and recipient, the use of apheresis to support new cellular approaches to cancer, the application of pathogen reduction for blood safety, the growth in plasma fractionation to meet the growing use of immune globulin preparations and other plasma-derived derivatives, as well as new approaches to support patients with massive bleeding, coagulopathy, and malignancy.

When the first edition was published, the transition away from whole blood to components and from cold-stored platelets to room-temperature stored platelets was nearly complete. Now we are seeing a reverse trend with recognition of potential benefits for the bleeding patient when treated with whole blood and cold-stored platelets. In the period since 1991, hemophilia care has gone from blood components such as cryoprecipitate, to plasma-derived factor concentrates, to recombinant products, to nonreplacement recombinant treatments, and finally to gene therapy to correct the defect that causes the disease. This is but one example of the evolution of the broader field of transfusion medicine we are capturing in this new sixth edition. We have assembled chapters and authors to guide the reader in understanding the changes that are occurring. At the same time, we have retained a significant amount of still-relevant material from earlier editions.

Contributors for this edition have once again been drawn from various scientific, medical, and surgical disciplines. Thus, this book encompasses topics including encouraging and managing donors, collecting and preserving donated blood, and matching each component to the appropriate recipient, based on the patient's clinical needs. The text also extends these concepts to tissue and goes beyond the field's basic tenets to address new applications.

We can think of no better way to honor Dr. Rossi's legacy than to present a sixth edition that blends transfusion science with clinical medicine, thus facilitating the thoughtful and measured prescription of blood, blood components, and their alternatives. Both the laboratory practice of blood banking and the clinical practice of transfusion medicine remain as important as ever. We proudly attribute the long-term influence of this field to its early leaders, who organized the discipline of transfusion medicine for success by anticipating future practice. We thank our new and returning contributors and the editorial staff at Wiley Blackwell for making possible a sixth edition of *Rossi's Principles of Transfusion Medicine* in this new pandemic-influenced world of transfusion practice.

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List of abbreviations

2RBC	double red cell collection
3-PCC / 3F-PCC	three-factor nonactived prothrombin complex concentrate
4-PCC / 4F-PCC	four-factor nonactived prothrombin complex concentrate
A3GALT2	isogloboside synthase
A4GALT1	PIPK synthase
AA	aplastic anemia
AABB	Association for the Advancement of Blood and Biotherapies (previously: American Association of Blood Banks)
AAP	American Academy of Pediatrics
aAPC	artificial antigen presenting cell
AATB	American Association of Tissue Banks
AAV	adeno-associated virus
AAV	ANCA-associated vasculitis
Ab	antibody
ABC	America's Blood Centers
ABC/EBA	America's Blood Centers/European Blood Alliance
ABE	acute bilirubin encephalopathy
ACCP	American College of Chest Physicians
ACD	acid citrate dextrose solution
ACD-A	acid-citrate-dextrose formula A
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACh	acetylcholine
AChE	acetylcholinesterase
AChR	acetylcholine receptor
ACI	anemia of chronic inflammation
ACKR1	atypical chemokine receptor 1
ACOG	American College of Obstetricians and Gynecologists
ACS	acute chest syndrome
ACT	activated clotting time
ADA	adenosine deaminase
ADCC	antibody-dependent cellular cytotoxicity
ADEM	acute disseminated encephalomyelitis
ADF	actin depolymerizing factor
aDHQ	Abbreviated Donor History Questionnaire
ADORA2b	Adenosine interactions with the receptor A2B
ADP	adenosine diphosphate
ADSC	adipose-derived stem cell
AECII	alveolar epithelial type cells of the upper airway II
AF	atrial fibrillation
AFSC	amniotic fluid-derived stem cells
AGM	aortogonadomesonephros
AHF	antihemophilic factor
AHG	antihuman globulin
AHPI	antihuman polyclonal immunoglobulin
AHSP	alpha-hemoglobin stabilizing protein
AHTR	acute hemophilic transfusion reaction
aHUS	atypical hemolytic-uremic syndrome
AIDS	acquired immune deficiency syndrome
AIHA	autoimmune hemolytic anemia
AIS	absent iron stores
AKI	acute kidney injury
ALAS2	5-aminolevulinic acid synthase
ALI	acute lung injury
ALL	acute lymphoblastic leukemia
ALT	alanine transferase
AML	acute myelogenous leukemia
AMP	adenosine monophosphate
AMPD	adenosine monophosphate deaminase
AMR	antibody-mediated rejection
AMR	Ashwell–Morell receptor
aMSCs	adipose tissue-derived mesencyhmal stem cells
ANC	absolute neutrophil count
ANCA	antineutrophil cytoplasmic antibodies
ANG1	angiopoietin 1
ANH	acute nonvolemic hemodilution
ANK1	ankyrin
anti-GBM	anti-glomerular basement membrane antibody
anti-Gov	anti-HPA-15 antibody
anti-TPO	antithyroid peroxidase
ANXA2	annexin 2
APC	antigen-presenting cell
aPCC	activated prothrombin complex concentrate
APCs	antigen-presenting cells
API	$alpha_1$-proteinase inhibitor
APS	antiphospholipid antibody syndrome
aPTT	activated partial thromboplastin time
AQP1	aquaporin-1
AQP3	aquaporin-3
AQP4-IgG	aquaporin-4 immunoglobulin G antibodies
ARC	absolute reticulocyte count
ARDS	acute respiratory distress syndrome
ARDS	adult respiratory distress syndrome
ARIPI	Age of Red Blood Cells in Premature Infants Study
ART	antiretroviral therapy
AS	additive solution
ASA	American Society of Anesthesiologists
ASFA	American Society for Apheresis
ASH	American society of Hematology
ASO	antisense oligonucleotides

ASP	antibody-specific prediction
ASPEN	association of sickle cell priapism, exchange transfusion and neurological events
ASRI	American Society for Reproductive Immunology
ASSC	acute splenic sequestration crisis
ASTCT	American Society for Transplantation and Cellular Therapy
AT	antothrombin
ATF4	activating transcription factor 4
ATG	antithymocyte globulin
ATIII	antithrombin III
ATL	adult T-cell leukemia and lymphoma
ATP	adenosine 5prime*-triphosphate
ATRs	allergic transfusion reactions
ATS	American Thoracic Society
AUC	area under the ROC curve
AUG	Augustine blood group
AvWS / AVWS	acquired von Willebrand syndromex
B-ALL	B-cell acute lymphoblastic leukemia
B-CAM	basal cell adhesion molecule
B-CAM/LU	Basal Cell Adhesion Molecule–Lutheran antigen
B3GALNT1	P synthase
B19V	parvovirus B19
BAGP	bicarbonate, adenine, glucose, and phosphate
BART	Blood Conservation Using Antifibrinolytics in a Randomized Trial
BasoEB	basophilic erythroblast
BB/TS	Blood Bank/Transfusion Medicine standards
BC method	buffy-coat method
BCEs	blood collection establishments
BCMA	B cell maturation antigen
BCSH	British Committee for Standards in Hematology
BCT	blood component therapy
BDD	B-domain-deleted
BECS	blood establishment computer software
BELIEVE	An Efficacy and Safety Study of Luspatercept Versus Placebo in Adults Who Require Regular Red Blood Cell Transfusions Due to Beta Thalassemia
BEN	benign ethnic neutropenia
BFU-Es	burst-forming units-erythroid
BFU-MK	burst-forming units-megakaryocyte
BiKE	bispecific killer engager
BIND	bilirubin-induced neurotoxicity
BloodNet	Pediatric Critical Care Blood Research Network
BM-MSCs	bone marrow-derived mesenchymal stem cells
BMD	Becker muscular dystrophy
BMI	body mass index
BMP	bone morphogenetic protein
BMSC	bone marrow stem cell
BMT	bone marrow transplantation
BNP	B-type natriuretic peptide
BOS	bronchiolitis obliterans syndrome
BP	blood pressure
BPAC	FDA Blood Products Advisory Committee
BPD	bronchopulmonary dysplasia
BRN	World Health Organization Blood Regulators Network
BSA	body surface area
BSE	bovine spongiform encephalopathy
BSS	Bernard Soulier syndrome
BT	bleeding time
BTHC	butyryl-tri-hexyl citrate
BVDV	bovine viral diarrhea virus
C/EBPα	CCAAT/enhancer binding protein α
CAAR	chimeric auto antigen receptor
CABG	coronary artery bypass graft
CAD	cold agglutinin disease
CAEV	arthritis-encephalitis virus of goats
CAFC	cobblestone area-forming cell
CALR	calreticulin
cAMP	cyclic adenosine monophosphate
CAP	College of American Pathologists
CAPS	catastrophic antiphospholipid syndrome
CAR	chimeric antigen receptor
CAR	CXCL12 abundant reticular (cell)
CAR-T cell	T cell expressing a chimeric antigen receptor
CARS	compensatory anti-inflammatory response syndrome
CASI	computer-assisted self-interview
CASPR2	contactin-associated protein-2
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CBF	cerebral blood flow
CBS	Canadian Blood Services
CCAD	Central Cardiac Audit Database
ccc-DNA	covalently closed circular DNA
CCI	corrected count increment
CCP	convalescent Covid plasma
CCPD	complement control protein domain
CDA	congenital dyserythropoietic anemia
CDC	Centers for Disease Control and Prevention
CDC	complement-dependent cytotoxicity
CDER	Center for Drug Evaluation and Research
CD–P–TS	European Committee on Blood Transfusion
CDR	complementarity-determining region
CDRH	Center for Devices and Radiologic Health
CDSS	clinical decision support systems
CERA	polyethylene glycol-conjugated recombinant human erythropoietin
CFB	complement factor B
cffDNA	cell-free fetal DNA
CFH	complement factor H
CFI	complement factor I
CFR	US Code of Federal Regulations
CFU-Es	colony-forming units-erythroid
CFU-GM	progenitor cells with the capacity to generate neutrophils in vitro
CFU-MK	colony-forming units-megakaryocyte
CGD	chronic granulomatous disease
cGMP	current good manufacturing practice
cGMP	cyclic guanosine monophosphate
CH2-THF	methylenetetrahydrofolate

CH3-THF	methyltetrahydrofolate
CHAPS	3-[(3-Cholamidopropyl) dimethylammonio]-1-propanesulfonate hydrate
CHCM	cell hemoglobin concentration mean
CHIKV	chikungunya virus
CHILL REDS-III	Comparison of Donation History and Iron Levels in Teenage Blood Donors
ChLIA	chemiluminescent immunoassays
CHMP	Committee for Medicinal Products for Human Use
CHO-THF	formyltetrahydrofolate
CHOP	Study of Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisone
CHr	cellular hemoglobin in reticulocytes
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
CIT	chemotherapy-induced thrombocytopenia
CJD	Creutzfeldt–Jakob disease
CKD	chronic kidney disease
CLET	cultured limbal epithelial transplantation
CLIA	chemiluminescent immunoassay
CLIA	Clinical Laboratory Improvement Act
CLL	chronic lymphoid leukemia
CM	carboxymethyl
CM-HUS	complement-mediated hemolytic-uremic syndrome
CM-TMA	complement-mediated thrombotic microangiopathy
CMIAs	chemiluminescent microparticle immunoassays
CML	chronic myelogenous leukemia
CMP	common myeloid precursor
CMQCC	California maternal quality care collaboration
CMS	Centers for Medicare and Medicaid Services
CMV	cytomegalovirus
CNS	central nervous system
CNSHA	chronic nonspherocytic hemolytic anemia
COBLT	Cord Blood Transplant (study)
CoE	Council of Europe
COM	All Common Checklist
COOP	continuity of operations plans
COX2	cyclooxygenase 2
CP2D	citrate phosphate double dextrose
CPB	cardiopulmonary bypass
CPD	citrate–phosphate–dextrose
CPDA	citrate–phosphate–dextrose–adenine
CPDA-1	citrate phosphate dextrose adenine
CPOE	computerized physician order entry systems
CPRA	calculated panel-reactive antibody tests
CPSI	Canadian Patient Safety Institute
CQ	clindamycin and quinine
CR	complete response
CR1	complement receptor 1
CRASH-2	Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage trial
CREG	cross-reactive group
CRISPR	clustered regularly interspaced short palindromic repeat
CRM	cross-reactive material
CRPS	chronic regional pain syndrome
CRPS II	chronic regional pain syndrome type 2
CRRT	continuous renal replacement therapy
CRS	cytokine release syndrome
CS	caesarean section
CSA	cyclosporine
CSF	circulating steel factor
CT	computerized tomography
CTA	cancer-testis antigen
CTCL	cutaneous T-cell lymphoma
CTL	cytotoxic T-cell
CTL2	choline transporter-like 2 protein
CTLA-4	cytotoxic T lymphocyte-associated protein 4
CTT	chronic transfusion therapy
cTTP	congenital thrombotic thrombocytopenic purpura
CVAD	central venous access device
CVCs	central venous catheters
CWD	chronic wasting disease
CXCL12	stromal-cell derived factor 1
CY	cyclophosphamide
DAF	decay accelerating factor
DAH	diffuse alveolar hemorrhage
DAMPs	damage-associated pattern molecules
DARC	Duffy antigen receptor for chemokines
DART	Danish Registration of Transfusion Accidents
DAT	direct antiglobulin test
dATP	deoxy adenosine triphosphate
DBA	Diamond–Blackfan anemia
DBCD	Division of Blood Components and Devices
DBM	demineralized bone matrix
DC	dendritic cell
DCASGPR	dendritic cell asialoglycoprotein receptor
DCM	dilated cardiomyopathy
DCs	dendritic cells
DD	D-dimers
DDAVP	desmopressin
DEA	diethyleneamine
DEAE	dietlylaminoethyl
DEC	diethylcarbamazine
dECM	decellularised extracellular matrix
DEHP	diethylhexyl phthalate
DEM	Donor Educational Materials
DETTD	Division of Emerging and Transfusion Transmitted Diseases
DF	dengue fever
DFO	deferoxamine B mesylate
DFP	deferiprone
DFPP	double-membrane filtration plasmapheresis
DFSD	dry fibrin sealant dressing
DFX	deferasirox
dGTP	deoxy guanine triphosphate
DHF	dihydrofolate
DHFR	dihydrofolate reductase
DHQ	Donor History Questionnaire
DHS	Department of Homeland Security

DHSt	dehydrated stomatocytosis
DHTF	Donor History Task Force
DHTRs	delayed hemolytic transfusion reactions
DIC	disseminated intravascular coagulation
DIIHA	drug-induced immune hemolytic anemia
DITP	drug-induced immune thrombocytopenic purpura
DLIs	donor lymphocyte infusions
DMD	Duchenne muscular dystrophy
DMH/DHA	dorsomedial nucleus/dorsal area
DMS	demarcation membrane system
DMSO	dimethyl sulfoxide
DOACs	direct oral anticoagulants
DOT	Department of Transportation
2,3-DPG	2,3-diphosphoglycerate
DSAs	donor-specific antibodies
DSBs	double-stranded breaks
dsDNA	double-stranded DNA
DSEK	Descemet's stripping endothelial keratoplasty
DSGG	disialogalactosylgloboside
dsRNA	double-stranded RNA
DSS	decision support system
DSTR	delayed serologic transfusion reaction
DTT	dithiothreitol
DVT	deep vein thrombosis
EACA	ε-aminocaproic acid
EBA	European Blood Alliance
EBI	erythroblastic island
EBV	Epstein–Barr virus
EC	endothelial cells
ECBS	Expert Committee on Biological Standardization
ECG	electrocardiogram
ECM	extracellular matrix
ECMO	extracorporeal membrane oxygenation
ECP	extracorporeal photopheresis
ECV	extracorporeal volume
EDQM	European Directorate for the Quality of Medicines
EDTA	ethylenediaminetetraacetic acid
EEA	European Economic Area
EFIC	exception from informed consent
EGC	endothelial glycocalyx
EGPA	eosinophilic granulomatosis with polyangiitis
EIA	enzyme immuno(sorbent) assay
EIAV	infectious anemia virus of horses
ELBW	extremely low birthweight
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMAs	emergency management agencies
EMCV	encephalomyocarditis virus
EMP3	epithelial membrane protein 3
EMP	Embden–Meyerhof–Parnas pathway
EMP	erythroblast-macrophage protein
ENT1	equilibrative nucleoside transporter 1
EP	European Pharmacopoeia
EP3Rs	prostaglandin EP3 receptors
EPO	erythropoietin
EPO-a	erythropoietin alpha
EPO-R	erythropoietin receptor
ePTFE	expanded polytetrafluorethylene
ERFE	erythroferrone
ERMAP	erythrocyte membrane-associated protein
ESAs	erythropoietin-stimulating agents
ESC	embryonic stem cell
ESF	Emergency Support Functions (NRF)
ESRD	end-stage renal disease
ET	essential thrombocythemia
ETTNO	Effect of Transfusion Thresholds on Neurocognitive Outcomes of extremely low birth weight infants Trial
EU	European Union
EUHASS	European Hemophilia Safety Surveillance
EV	extracellular vesicles
EVA	ethylene vinyl acetate
EXM	electronic crossmatch
EXT	extreme thrombocytosis
FACT	Foundation for the Accreditation of Cellular Therapy
FADH	reduced flavin adenine dinucleotide
FAST	focused ultrasonographic survey for trauma
FBS	fetal blood sampling
FC	fibrinogen concentrates
fCJD	familial Creutzfeldt–Jacob disease
FCR	fraction of cells remaining
FcRn	neonatal Fc receptor
FDA	United States Food and Drug Administration
FDAAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FDASIA	Food and Drug Administration Safety and Innovation Act
FDC	follicular dendritic cell
FDCA	Food, Drug, and Cosmetic Act
FDCs	follicular dendritic cells
FDP	fibrin degradation product
FEIBA	factor VIII inhibitory bypass activity
FEMA	Federal Emergency Management Agency
FEP	free erythrocyte protoporphyrin
FFI	fatal familial insomnia
FFP	fresh frozen plasma
FGS	focal glomerulosclerosis
FH	familial hypercholesterolemia
FL	Flt3-ligand
FLAER	fluorescent aerolysin
FLIPID	Ferritin Levels in Plasma Donors study
FMH	fetal–maternal hemorrhage
FNAIT	fetal/neonatal alloimmune thrombocytopenia
FNHTR	febrile nonhemolytic transfusion reaction
FOCUS	Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair study
FSFI	Female Sexual Function Index
FSGS	focal segmental glomerulosclerosis
FSPT	filtered sunlight phototherapy

FT/RA	first-time and reactivated (donors)
FTA-ABS	fluorescent *Treponema pallidum* antibody absorption
G-CSF	granulocyte colony-stimulating factor
G6PD	glucose-6-phosphate dehydrogenase
GABA	γ-amino butyric acid
GAD-65	65-kD isoform of glutamic acid decarboxylase
GAG	glycoslyaminoglycan
Gal	β-galactose
GalNAc	*n*-acetylgalactosamine
GATA1	GATA-binding factor 1
GBM	glomerular basement membrane
GBS	Guillain–Barr´¿¢ syndrome
GDF	growth differential factor
GDP	guanosine diphosphate
GEF-H1	guanine nucleotide exchange factor H1
GEMM-CFC	granulocyte-erythroid-macrophage-megakaryocyte colony-forming cells
GEN	Laboratory General Checklist
GFI1	growth factor interdependent 1
GI	gastrointestinal
GLUT1	glucose transporter 1
GM-CSF	granulocyte macrophage colony-stimulating factor
GMP	good manufacturing practice
GP	glycoprotein
GPA	glycophorin A
GPA	granulomatosis with polyangiitis
GPB	glycophorin B
GPC	glycophorin C
GPCR	guanine nucleotide-binding protein-coupled receptor
GPD	glycophorin D
GPI	glycosylphosphatidylinositol
GPS	Goodpasture syndrome
GPVI	Glycoprotein VI (platelet)
GPX4	glutathione peroxidase 4
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSH	glutathione
GSL	glycospingolipid
GSS	Gerstmann–Straussler–Scheinker disease
GT	gestational thrombocytopenia
GT6	glycosyltransferase family 6
GTA	A-transferase
GTB	B-transferase
GTP	guanosine triphosphate
GTX	granulocyte transfusions
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia
GWA	genome-wide association
HA	hyaluronic acid
HA	hydroxyapatite
HAA	hospital-acquired anemia
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HB-PAN	hepatits B-associated polyarteritis nodosa
HbAA	normal hemoglobin A
HbAS	hemoglobin A sickle
HbC	hemoglobin C
HBc	hepatitis B core
HBcAg	hepatitis B core antigen
HbD	hemoglobin D
HbE	hemoglobin E
HBeAg	hepatitis B e antigen
HbF	fetal hemoglobin
HBOCs	hemoglobin-based oxygen carriers
HbS	hemoglobin S
HBSAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCEC	human corneal endothelial cell
HCT	hematopoietic cell transplant
HCT/P	human cells, tissues, and cellular and tissue-based product
HCV	hepatitis C virus
HDFN	hemolytic disease of the fetus and newborn
HDI	human development index
HDIVIG	high-dose intravenous immunoglobulin
HDL	high-density lipoprotein
HDN	hemolytic disease of the fetus and newborn
HDR	homology-directed repair
HDV	hepatitis D virus
HE	hereditary elliptocytosis
HEIRS	REDS-III Hemoglobin and Iron Recovery Study
HELLP (syndrome)	hemolysis, elevated liver enzymes, and low platelets
HEMPAS	Hereditary erythroblastic multinuclearity with positive acidified serum lysis test
HES	hydroxyethyl starch human
hESC	human embryonic stem cell
HEV	hepatitis E virus
HFMEA	Healthcare Failure Mode and Effect Analysis
Hgb	hemoglobin
hGH	human growth hormone
HH	hereditary hemochromatosis
HHV	human herpesvirus
HIC	hydrophobic interaction chromatography
HIF	hypoxia-inducible transcription factor
HIF-PHDs	hypoxia-inducible transcription factor prolyl hydroxylases
HIPA	heparin-induced platelet activation assay
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLH	hemophagocytic lymphohistiocytosis
HMW	high molecular weight
HMWK	high-molecular-weight kininogen
HNA	human neutrophil antigen
HNA-3	human neutrophil antigen 3
HO1	heme oxygenase-1
HPAs	human platelet antigens
HPC	hematopoietic progenitor cell
HPCT	hematopoietic progenitor cell transplantation
HPP	hereditary pyropoikilocytosis
HPV	human papilloma virus
HR	hazard ratio
HRI	heme-regulated inhibitor

HRP	histidine-rich protein 2
HSC	hematopoietic stem cells
HSCT	hematopoietic stem cell transfusion
HSV	herpes simplex virus
HTA	health technology assessment
HTLV	human T-cell lymphotropic virus
HTR	hemolytic transfusion reaction
hUCMSCs	human umbilical cord mesenchymal stem cells
HUS	hemolytic-uremic syndrome
HVM	handheld vital microscopy
hWJCs	Wharton's jelly-derived mesenchymal stem cells
HX	hereditary xerocytosis
%HYPOm	percentage of hypochromic mature red blood cells
%HYPOr	percentage of hypochromic red blood cells
IA-HUS	infection-associated hemolytic-uremic syndrome
IAP	integrin-associated protein
IAT	indirect antiglobulin test
IBCT	incorrect blood component transfused
IBR	intraoperative blood recovery
IC	informed consent
ICAM4	interstitial cell adhesion molecule-4
ICCBBA	International Council for Commonality in Blood Banking Automation
ICH	International Conference on Harmonization (of Technical Requirements)
ICH	intracranial hemorrhage
iCJD	iatrogenic Creutzfeldt–Jakob disease
ICU	intensive care unit
ID NAT	individual nucleic acid test
IDA	iron-deficiency anemia
IDE	iron-deficient erythropoiesis
IDH1	isocitrate dehydrogenase 1
IDSA	Infectious Disease Society of America
IDT	individual testing
IE	ineffective erythropoiesis
IFA	immunofluorescence assay
IFAT	immunofluorescent antibody test
IFN	interferon
IG/ Ig	immunoglobulin
IgA	immunoglobulin A
IGF-1-R	insulin-like growth factor 1 receptor
IGF1	insulin-like growth factor-1
IgG	immunoglobulin G
IgM	immunoglobulin M
IgSF	immunoglobulin superfamily
IHD	incorporating isovolemic hemodilution (red cell exchange)
IHN	International Hemovigilance Network
IL	interleukin
IM	intramuscular
IMP	inosine monophosphate
IND	individual donor
IND	investigational new drug
iNKT	invariant natural killer T cell
INR	international normalized ratio
IPC	immature platelet count
IPD	individual-patient data
IPF	immature platelet fraction
IPFA	International Plasma Fractionation Association
iPSC	induced pluripotent stem cell
IPSS	International Prognostic Scoring System
IQPP	International Quality Plasma Program
IR	interventional radiologists
IRE	iron-responsive element
IRP	iron regulatory protein
ISBT	International Society of Blood Transfusion
ISTARE	International Surveillance Database for Transfusion Adverse Reactions and Events
ISTH	International Society on Thrombosis and Hemostasis
IT	information technology
ITAC	Inpatient Treatment With Anti-Coronavirus Immunoglobulin Trial
ITI	immune tolerance induction
ITP	immune thrombocytopenic purpura
iTTP	immune thrombotic thrombocytopenic purpura
IV	intravenous
IVC	inferior vena cava
IVD	in vitro diagnostic devices
IVIG / IVIg	intravenous immunoglobulin
JAK2	Janus kinase 2
KIR	killer immunoglobulin-like receptor
KLF-1	Kr?ppel-like factor-1
LacCer	lactosylceramide
LAD	leukocyte adhesion deficiency
LAG3	lymphocyte-activation gene 3
LAK	lymphokine-activated killer
LCL	lymphoblastoid line
LCMV	lymphatic choriomeningitis
LCR	locus control region
LCT	lymphocytotoxicity
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LEMS	Lambert–Eaton myasthenic syndrome
LESC	limbal epithelial stem cell
LF	low ferritin
LFI	lateral flow immunoassay
LGI1	leucine-rich glioma inactivated 1
LGL	large granular lymphocyte
LHDAg	long hepatitis D antigen
LHR	long homologous repeat
LIA	latex-enhanced immunoturbidimetric assay
LIC	liver iron concentration
LIF	leukemia inhibitory factor
LISS	low ionic strength solution
LKE	luke antigen on erythrocytes
LMAN	lectin mannose binding
LMO2	Lim domain partner of TAL1
LMW	low molecular weight
LMWH	low molecular weight heparin
lncRNAs	long noncodiding RNAs
LP	liquid plasma
LPI	labile plasma iron
LPS	lipopolysaccharide
LR	leukocyte reduction / leukoreduced
LRP4	lipoprotein receptor-related protein 4

LSC	limbal stem cell
LTA	lipoteichoic acid
LTOWB	low-titer group O whole blood
LVDS	large volume delayed sampling
LVEF	left ventricular ejection fraction
Mab	monoclonal antibody
MAC	membrane attack complex
McC	McCoy antigen
MACE	modified capture enzyme-linked immunosorbent assay
MAG	myelin-associated glycoprotein
MAHA	microangiopathic hemolytic anemia
MAIPA	monoclonal antibody-specific immobilization of platelet antigens
MAP	mean arterial pressure
MAPK	mitogen-activated protein kinase
MART	melanoma antigen recognized by T cells
MATTERs	Military Application of Tranexamic acid in Trauma Emergency Resuscitation study
MB	methylene blue
MBFs	microaggregate blood filters
MBG	Marburg virus
MBP	myelin basic protein
MCA	middle cerebral arteries
MCFD	multiple coagulation factor deficiency gene
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCP	macrophage chemoattractant protein
MCV	mean corpuscular volume
MDDS	Medical Device Data Systems
MDH1	malate dehydrogenase 1
MDL	Medication Deferral List
MDS	myelodysplastic syndrome
MECOM	MDS1 and EV11 complex locus protein
MEDALIST	A Study of Luspatercept to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes
MEHP	mono(2-ethylhexyl) phthalate
MEP	megakaryocytic-erythroid progenitor
MET	mesenchymal–epithelial transition
MFI	mean fluorescence intensity
MGSA	melanocyte growth-stimulating activity
MGUS	monoclonal gammopathy of undetermined significance
MHA-TP	Microhemagglutination Assay for *Treponema pallidum*
MHC	major histocompatibility complex
MIRL	membrane inhibitor of reactive lysis
miRNA	micro RNA
MK	megakaryocyte
MKL	myocardin-like transcription factors
MLR	mixed lymphocyte reaction
MM	multiple myeloma
MMN	multifocal motor neuropathy
MMP	matrix metalloproteinase
MMR	Measles, mumps, and rubella vaccination
MnPO	median preoptic area
MoAbs	monoclonal antibodies
MODS	multiple-organ dysfunction syndrome
MOF	multiple-organ failure
MOG	myelin oligodendrocyte glycoprotein
8-MOP	8-methyoxypsoralen
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MPP	multipotent progenitor
MPV	mean platelet volume
MR	magnetic resonance
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
MSC	mesenchymal stem (stromal) cell
MSM	men who have sex with men
MTP	massive transfusion protocol
MTX	methotrexate
MuSK	muscle-specific kinase
MVM	minute virus of mice
NAAT	nucleic acid amplification testing
NACSSG	National Acute Chest Syndrome Study Group
NAD	nicotinamide adenine dinucleotide
NADH	reduced nicotinamide adenine dinucleotide
NADP	nicotinamide adenine dinucleotide phosphate
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NAIT	neonatal alloimmune thrombocytopenia
NAITP	neonatal alloimmune thrombocytopenic purpura
NANB	non-A, non-B hepatitis
NAPTT	non-activated partial thromboplastin time
NAT	nucleic acid testing
NATA	Network for Advancement of Transfusion Alternatives
NBCUS	National Blood Collection and Utilization Survey
NCAs	national competent authorities
NCI	National Cancer Institute
NDDR	National Donor Deferral Registry
NDI	neurodevelopmental impairment
NDMA	nitrosodimethylamine
NEC	necrotizing enterocolitis
NETs	neutrophil extracellular traps
NF-kB	nuclear factor κB
NFE2	nuclear factor, erythroid 2
NGC	nerve guidance conduits
NGS	next-generation sequencing
NHLBI	National Heart, Lung, and Blood Institute
NHS	National Health Service (UK)
NHSBT	National Health System Blood and Transplant Service
NHSN	National Healthcare Safety Network
NIBSC	National Institute of Biological Standards and Control
NICU	neonatal intensive care unit
NIH	National Institutes of Health
NIRS	near-infrared spectroscopy
NK	natural killer
NMDAR	*N*-methyl-D-aspartate receptor
NMDP	National Marrow Donor Program
NMOSD	neuromyelitis optica spectrum disorder
NNNI	Northern Neonatal Nursing Initiative

NO	nitric oxide
NOD	non-obese diabetic
Nplate	Romiplostim
NPO	nil per os
NRAs	National Regulatory Authorities
NRC	Nuclear Regulatory Commission
NRF	National Response Framework
NSAID	nonsteroidal anti-inflammatory drug
NTBI	non-transferrin-bound iron
NTDT	nontransfusion-dependent thalassemia
NTT	number needed to treat
NYHA	New York Heart Association
OBI	occult hepatitis B infection
OBRR	Office of Blood Research and Review
OCS	open canalicular system
OEF	oxygen extraction fraction
OGP	osteogenic growth peptide
OHI	occult hepatitis infection
OHSt	overhydrated hereditary stomatocytosis
OMCL	Official Medicines Control Laboratory
OPN	osteopontin
OR	odds ratio
ORC	oxidized regenerated cellulose
OrthoEB	orthochromatic erythroblast
OSHA	Occupational Safety and Health Administration
OTAT	Office of Tissues and Advanced Therapies
OthoEBs	orthochromatic erythroblasts
P-OH	prolyl hydroxylation
PAB	pseudoautosomal boundary
PAF	platelet-activating factor
PAGGGSM	phosphate-adenine-glucose-guanosine-gluconate-saline-mannitol
PAGGSM	phosphate-adenine-glucose-guanosine-saline-mannitol
PaGIA	particle gel immunoassay
PAH	pulmonary arterial hypertension
PAI-1	plasminogen activator inhibitor type 1
PAIgG	platelet-associated IgG
PALISI	Pediatric Acute Lung Injury and Investigators Network
PAN	polyarteritis nodosa
PANDAS	pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PAR1	pseudoautosomal region 1
PAS	platelet additive solution
PASSPORT	Post Approval Surveillance Study of Platelet Outcomes, Release Tested (protocol)
PAT	passive alloimmune thrombocytopenia
PBM	patient blood management
PBMC	peripheral blood mononuclear cell
PBPC	peripheral blood progenitor cell
PBR	postoperative blood recovery
PBSC	peripheral blood stem cell
PC	platelet concentrate
PCAM	platelet-endothelial cell adhesion molecule-1
PCC	prothrombin complex concentrates
PCH	paroxysmal cold hemoglobinuria
PCL	polycaprolactone
PCP	*pneumocystis pneumonia carnii*
PCR	polymerase chain reaction
PCSK9	proprotein convertase subtilisin-kexin type 9
PD-1	programmed cell death protein 1
PDE	phosphodiesterase
pdFVII	plasma-derived factor VII
pdFX	plasma-derived factor X
pdFXIII	plasma-derived factor XIII
PDGF-B	Platelet-derived growth factor subunit B
PDLLA	poly-D,L-lactide
PDMP	plasma-derived medicinal product
PEA	P-selectin expression assay
PEG	polyethylene glycol
PEG-rHuMGDF	pegylated recombinant human megakaryocyte growth and development factor
PEI	Paul Ehrlich Institute
PENUT	Preterm Erythropoetin Neuroprotection Trial
PF	platelet factor
PF4	platelet factor 4
PF24	24-hour frozen plasma
PFA-100	platelet function analyzer 100
PfEMP(-1)	*Plasmodium falciparum* erythrocyte membrane protein(-1)
PGA	poly(glycolic acid)
PGE2	prostaglandin E2
PhEur	European Pharmacopeia
PHS	Public Health Service
PHSA	Public Health Service Act
PI	platelet increment
PI3K	phosphatidylinositol-3-kinase
PIC/S	Pharmaceutical Inspection Co-operation Scheme and Pharmaceutical Inspection Convention
PICC	peripherally inserted central catheter
PIG-A	phosphatidylinositol glycan class A
PINT	Premature Infants in Need of Transfusion Study
PIV	peripheral intravenous
PIVKAs	proteins induced in vitamin K absence
PK	penetrating keratoplasty
PKA	protein kinase A
PKD	pyruvate kinase deficiency
PLA	poly(lacticacid)
PLADO	Optimal Platelet Dose Strategy to Prevent Bleeding in Thrombocytopenia Patients
PLC	poly(caprolactone)
PLGA	poly(lactic-co-glycolic acid)
PLS	passenger lymphocyte syndrome
PME	partial mutual exchange
PMMA	polymethylmethacrylate
PMN	polymorphonuclear neutrophil
PNH	paroxysmal nocturnal hemoglobinuria
PNI	peripheral nerve injury
PNM	neutrophil
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes (syndrome)

POISE / POISE-2	Perioperative Ischemic Evaluation trial
PolyEB	polychromatophilic erythroblast
PPH	postpartum hemorrhage
PPi	pyrophosphate
PPP	pentose phosphate pathway
PPR	percent platelet recovery
PPTA	Plasma Protein Therapeutics Association
PR	pathogen reduction
PR3	proteinase 3
PRA	panel-reactive antibody tests
PRAC	Pharmacovigilance Risk Assessment Committee
PRBCs	packed red blood cells
PRCA	pure red blood cell aplasia
PRES	posterior leukoencephalopathy
ProEB	proerythroblast
PROMMTT	Prospective Observational Multicenter Massive Transfusion Trial
PROPPR	Pragmatic Randomized Optimal Plasma and Platelet Ratios trial
PRP	platelet-rich plasma
PrP^C	membrane-bound prion protein
PRPP	phosphoribosyl pyrophosphate
PRT	Pathogen Reduction Technology
PRV	pseudorabies virus
PS	phosphatidylserine
PSA	prostate-specific antigen
PSGL1	platelet sialoglycoprotein ligand-1
PSOs	patient safety organizations
PSV	peak systolic velocity
PT	prothrombin time
PTFE	polytetrafluoroethylene
PTLD	posttransplant lymphoproliferative disease
PTP	post-transfusion purpura
PTR	platelet transfusion refractoriness
PTT	partial thromboplastin time
PUP	previously untreated patient
PVC	polyvinyl chloride
PvDBP	P. vivax Duffy binding protein
PVH	hypothalamic paraventricular nucleus
pVHL	von Hippel–Lindau protein
PVR	poliovirus receptor
QA	quality assurance
QAE	quaternary amino ethyl
QALY	quality-adjusted life years
QC	quality control
RA	rheumatoid arthritis
RANTES	regulated on activation, normal T-cell expressed and secreted
RBCCs	red blood cell concentrates
RBC(s)	red blood cells
RBDM	risk-based decision-making
RBM15	RNA binding motif protein 15
RCAS1	receptor-binding cancer antigen expressed on SiSo cells
RCDADs	relevant communicable disease agents or diseases
RCE	red cell exchange
RE-LY	Randomized Evaluation of Long-Term Anticoagulant Therapy trial
REACT	Renal Autologous Cell Therapy
RECESS	Red Cell Duration Study
REDS-III	Recipient Epidemiology and Donor Evaluation Study-III
REF	febrile nonhemolytic transfusion reaction
rFIX	recombinant factor IX
RFLP	restriction fragment length polymorphism
rFVIIa	recombinant activated factor VII
rFVIII	recombinant factor VIII
RhAG	Rh-associated glycoprotein
RhD	rhesus D protein
rhEPO	recombinant human erythropoietin
RhIG	Rh immune globulin
RhoA	Ras homolog family member A
rhTPO	recombinant human thrombopoietin
rHuEPO	Recombinant human erythropoietin
RING	Safety and Effectiveness of Granulocyte Transfusion in Resolving Infection in People with Neutropenia study
RIPA	radioimmunoprecipitation assay
RIR	replication-incompetent retrovirus
RISE study	Retrovirus Epidemiology and Donor Study
RLS	reporting and learning systems
ROC	receiver operating characteristic
ROS	reactive oxygen species
ROTEM	rotational thromboelastometry
RP	reticulated platelet
RPa	raphe pallidus nucleus in the medulla
RPR	rapid plasma reagin
RPs	reticulated platelets
RR	repeat reactive
RSV	respiratory syncytial virus
RT	room temperature
RTTIs	relevant transfusion-transmitted infections
rVIIa	recombinant activated factor VII
rVWF	recombinant von Willebrand factor
S/D	solvent and detergent
S1P	sphingosine-1-phosphate
SAA	severe aplastic anemia
SABM	Society for the Advancement of Blood Management
SAG	saline, adenine, and glucose
SAG-M	saline, adenine, and glucose with mannitol
SAL	sterility assurance level
SAO	Southeast Asian Ovalocytosis
SBDS	Shwachman–Bodin–Diamond syndrome
SC	subcutaneous
sc-TPA	single-chain tissue plasminogen activator
sc-UPA	single-chain urokinase plasminogen activator
SCD	sickle cell disease
SCF	stem cell factor
scFv	single-chain variable fragment
SCI	silent cerebral infarcts
SCID	severe combined immunodeficiency
SCIG	subcutaneous IgG
sCJD	sporadic Creutzfeldt-Jakob disease
SCL	stem cell leukemia
SCN	severe congenital neutropenia
SCs	Schwann cells
SDF-1	stromal-cell-derived factor 1
SDS	sodium dodecyl sulfate

SDS-PAGE	sodium dodecyl sulfate-polyacrylamide gel electrophoresis
Se	secretor-positive
SHDAg	short Hepatitis D antigen
SHOT	Serious Hazards of Transfusion program (UK)
shRNA	short hairpin RNA
SID	Sd^a antigen
SID	secondary immune deficiencies
SINV	Sindbis virus
siRNA	small interfering RNA
SIRS	systemic inflammatory response syndrome
SIS	small intestinal submucosa
SIT trial	Silent Infarct Transfusion trial
Sl	Swain-Langley antigen
SLE	systemic lupus erythematosus
SMC	smooth muscle cell
SNO-Hb	*S*-nitrosohemoglobin
SNP	single nucleotide polymorphism
SNV	single nucleotide variation
SoGAT	International Working Group on the Standardization of Genomic Amplification Techniques for the Virological Safety Testing of Blood and Blood Products
SOP	standard operating procedure
SP	source plasma
SP	sulfopropyl
SPRCA	solid-phase red cell adherence
SPS	stiff-person syndrome
SQUID	superconducting quantum interference device
SRA	serotonin-release assay
SRF	serum response factor
SSCs	spermatogonial stem cells
ssDNA	single-stranded DNA
SSOP(H)	sequence-specific oligonucleotide probe hybridization
SSP(-PCR)	sequence-specific primer polymerase chain reaction
ssRNA	single-stranded RNA
STAT(5)	signal transduction and activator of transcription(-5)
sTfR	soluble transferrin receptor
STOP	Stroke Prevention Trial in Sickle Cell Anemia Trial
STOP 2	Optimizing Primary Stroke Prevention in Sickle Cell Anemia Trial
STS/SCA	Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists
Stx	shigatoxins
suPAR	soluble urokinase plasminogen activator receptor
SVC	superior vena cava
SWiTCH	Stroke With Transfusions Changing to Hydroxyurea trial
Syk	spleen tyrosine kinase
t-PA	tissue-type plasminogen-activator
TA-GVHD	transfusion-associated graft-versus-host disease
TA-MC	transfusion-associated microchimerism
TACO	transfusion-associated circulatory overload
TAD	transfusion-associated dyspnea
TAFI	thrombin-activatable fibrinolysis inhibitor
TALENs	transcription activator-like effector nucleases
TAMMv	timed average mean maximum velocity
TAPS	Transfusion Alternatives Preoperatively in Sickle cell disease trial
TAPS	twin anemia-polycythemia sequence
TAXI	Pediatric Critical Care Transfusion and Anemia EXpertise Initiative
TBSA	total body surface area
tc-TPA	two-chain tissue plasminogen activator
tc-UPA	two-chain urokinase plasminogen activator
TCD	transcranial Doppler ultrasound
TCP	tricalcium phosphate
TCR	T-cell receptor
TDT	Transfusion-dependent thalassemia
TEE	thromboembolic event
TEG	thromboelastography
TEVG	tissue-engineered vascular graft
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TGA	thrombin generation assay
TGF(-β)	transforming growth factor(-β)
Th	T helper (cell)
THA	total hip arthroplasty
THBD	Thrombomodulin
THF	tetrahydrofolate
TI	tincture of iodine
TIL	tumor-infiltrating lymphocyte
TIM3	T-cell immunoglobulin and mucin domain containing-3
TITRe2	The Transfusion Indication Threshold Reduction trial
TJC	The Joint Commission
TLR	toll-like receptor
TM	thalassemia major
TMAA	thrombotic microangiopathic anemia
TMA	thrombotic microangiopathy
TMA	transcription-mediated amplification
TMER	Transfusion Medicine Epidemiology Review study
Tmod1	modulatory T cell 1
TNC	total nucleated cell count
TNF	tumor necrosis factor
TNFα	tumor necrosis factor-α
TOP	transfusion of prematures study
TOPIC	Transfusion of Fresh Frozen Plasma in Nonbleeding ICU Patients trial
TOTM	triethyl hexyl trimellitate
TP	*Treponema pallidum*
tPA	tissue plasminogen activator
TPB	theory of planned behavior
TPE	therapeutic plasma exchange
TPMT	thiopurine methyltransferase
TPO	thrombopoietin
TPO-RAs	thrombopoietin receptor agonists
TRAIL	tumor necrosis factor-related apoptosis-inducing ligand

TRALI	transfusion-related acute lung injury
TRAP	Trial to Reduce Alloimmunization to Platelets
Treg	regulatory T cell
TRICC	Transfusion Requirements in Critical Care
TRICK	transfusion-related inhibition of cytokines
TRIM	transfusion-related immunomodulation
TRIPICU	Transfusion Strategies for Patients in Pediatric Intensive Care Units study
TRS	Technical Report Series (WHO)
TSEs	transmissible spongiform encephalopathies
TSO	Transfusion Safety Office
TSOs	transfusion safety officers
TSP	tropical spastic paraparesis
TT	thrombin time
TT-CMV	transfusion-transmitted cytomegalovirus infection
TTB	transfusion-transmitted babesiosis
TTD	transfusion transmitted disease
TTI	transfusion-transmissible infection
TTISS	Transfusion Transmitted Injuries Surveillance System
TTM	transfusion-transmitted malaria
TTP	thrombotic thrombocytopenic purpura
TTTS	twin-to-twin transfusion syndrome
TTV	TT virus
TTVIs	transfusion-transmitted viral infections
TWEAK	TNF-like weak inducer of apoptosis
TWiTCH	transcranial Doppler ultrasound With Transfusions Changing to Hydroxyurea trial
TXA	tranexamic acid
UBC / UCB	umbilical cord blood
UDHQ	Uniform Donor History Questionnaire
UEA	*Ulex europeaus*
UFH	unfractionated heparin
ULR	universal leukocyte reduction
UNOS	United Network for Organ Sharing
USP	US Pharmacopoeia and National Formulary
UTR	untranslated region
UV-A	ultraviolet A
UV-B	ultraviolet B
UV-C	ultraviolet C
VATS	Viral Activation by Transfusion Study
VCAM1	vascular cell adhesion molecule 1
vCJD	variant Creutzfeld–Jakob disease
VECs	vascular endothelial cells
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VGCC	voltage-gated calcium channel
VGKC	voltage-gated potassium channel
VIP	von Willebrand Disease International Prophylaxis study
VITT	vaccine-induced immune thrombotic thrombocytopenia
VKA	vitamin K antagonists
VKDB	vitamin K deficiency bleeding
VKDFs	vitamin K-dependant coagulation factors
VKOR	vitamin K epoxide reductase
VLBW	very-low-birthweight
VLDL	very-low-density lipoprotein
VML	volumetric muscle loss
VMV	visna-maedi virus of sheep
VOC	vaso-occlusive crisis
VP	viral structure protein
VPS	vascular positioning system
VSMCs	vascular smooth muscle cells
VWD / VWD	von Willebrand disease
vWF	von Willebrand factor
VXM	virtual crossmatch
WAIHA	warm autoimmune hemolytic anemia
WAS	Wiskott–Aldrich syndrome
WB	Western blot
WB	whole blood
WBC	white blood cell
WBD	whole blood derived
WBDPs	whole blood derived platelets
WBIT	wrong blood in tube
WCC	WHO Collaborating Center
WFH	World Federation of Hemophilia
WHIM (syndrome)	warts, hypogammaglobulinemia, infections, and myelokathexis
WHO	World Health Organization
WNV	West Nile virus
WOMAN	World Maternal Antifibrinolytic trial
ZFN	zinc finger nuclease
ZIKV	Zika virus
ZnPP	zinc protoporphyrin

About the companion website

This book is accompanied by a companion website.

www.wiley.com/go/simon/Rossi6

The website features:

- The figures from the book in downloadable PowerPoint slides.
- Downloadable PDFs of the complete reference lists from the book.

The password for the website is the first word of Chapter 1. Please use all lowercase.

SECTION I

Transfusion medicine from ancient times to the current pandemic

CHAPTER 1

Transfusion in the new millennium

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Prehistoric man left drawings of himself pierced by arrows.[1] This means he was as aware of blood as he was of his own limbs. The flint implements he used as tools and weapons distinguished him from other creatures and contributed to the violence of his era. As he hunted food and fought enemies, he observed bleeding and the properties of blood. A cut, received or inflicted, yielded a vivid red color. If the cut was shallow, there was little blood. But if the cut was deep, a red torrent flowing from the stricken victim quickly led to death, with shed blood congealed and darkening in the sun. Fatal hemorrhage was commonplace. Nonetheless, the sight must have been fearful and possibly existential as life flowed red out of the body of an enemy or a wounded animal.[2] It is no wonder, then, that at the dawn of recorded history, blood was already celebrated in religious rites and rituals as a life-giving force.

The cultural expressions of primitive and ancient societies, although separated by time or space, can be strikingly similar. Whether these expressions emerged independently or were diffused about the world by unknown voyagers will probably always remain clouded in mystery.[2] Nonetheless, there is a common thread in the ancient rituals that celebrate blood as a mystical vital principle. In Leviticus 17:11, "the life of the flesh is in the blood," and the Chinese Neiching (circa 1000 BCE) claims the blood contains the soul.[2] Pre-Columbian North American Indians bled their bodies "of its greatest power" as self-punishment,[3] Egyptians took blood baths as a recuperative measure, and Romans drank the blood of fallen gladiators in an effort to cure epilepsy.[4]

The Romans also practiced a ceremony called taurobolium—a blood bath for spiritual restoration. A citizen seeking spiritual rebirth descended into a pit or *fossa sanguinis*. Above him on a platform, a priest sacrificed a bull, and the animal's blood cascaded down in a shower upon the beneficiary. Then, in a powerful visual image, the subject emerged up from the other end of the pit, covered with blood and reborn.[1]

The legend of Medea and Aeson taken from Ovid's *Metamorphoses* and quoted in Bulfinch's *Mythology*[5] also ascribed rejuvenating powers to blood. Jason asked Medea to "take some years off his life and add them to those of his father Aeson." Medea, however, pursued an alternative course. She prepared a cauldron with the blood of a sacrificed black sheep. To this, she added magic herbs, hoarfrost gathered by moonlight, the entrails of a wolf, and many other things "without a name." The boiling cauldron was stirred with a withered olive branch, which became green and full of leaves and young olives when it was withdrawn. Seeing that all was ready,

> Medea cut the throat of the old man and let out all his blood, and poured into his mouth and into his wound the juices of her cauldron. As soon as he had imbibed them, his hair and beard laid by their whiteness and assumed the blackness of youth; his paleness and emaciation were gone; his veins were full of blood, his limbs of vigour and robustness. Aeson is amazed at himself and remembers that such as he now is, he was in his youthful days, 40 years before.

This legend seems to echo the apocryphal story of Pope Innocent VIII, who is said to have received the blood of three young boys in 1492 while on his deathbed. As the story goes, a physician attempted to save the pope's life by using blood drawn from three boys 10 years of age, all of whom died soon thereafter. Some nineteenth-century versions of this tale suggest the blood was transfused. However, earlier renditions more plausibly suggest that the blood was intended for a potion to be taken by mouth. In any event, there is no evidence the pope actually received any blood in any form.[6,7]

The folklore that flowed with blood was not accompanied by a great deal of accurate information. The ancient Greeks believed that blood formed in the heart and passed through the veins to the rest of the body, where it was consumed. Arteries were part of an independent system transporting air from the lungs. Although Erasistratos (circa 270 BCE) had imagined the heart as a pump, his idea was ahead of its time. As long as veins and arteries were dead-end channels transporting blood and air, there was little need for a pump in the system. Although Galen (131–201 CE) finally proved that arteries contain blood, communication with the venous system was not suspected. Blood, formed in the liver, merely passed through the blood vessels and heart on its way to the periphery.[1] These teachings remained in place for 1400 years until they were swept away in 1628 by Harvey's discovery of the circulation.

The realization that blood moved in a circulating stream opened the way to experiments on vascular infusion. In 1642, George von Wahrendorff injected wine[8]—and, in 1656, Christopher Wren and Robert Boyle injected opium and other drugs[9]— intravenously into dogs. The latter studies, performed at Oxford, were the inspiration for Richard Lower's experiments in animal transfusion.

Rossi's Principles of Transfusion Medicine, Sixth Edition. Edited by Toby L. Simon, Eric A. Gehrie, Jeffrey McCullough, John D. Roback, and Edward L. Snyder.

Companion website: www.wiley.com/go/simon/Rossi6

The first animal transfusion

Richard Lower (1631–1691) was a student at Oxford when Christopher Wren and Robert Boyle began their experiments on infusion. In due course, Lower joined their scientific group and studied the intravenous injection of opiates, emetics, and other substances into living animals.[10] In time, the transfusion of blood itself became the objective. The announcement of the first successful transfusion, performed by Richard Lower at Oxford in February 1665, was published on November 19, 1666, in the *Philosophical Transactions of the Royal Society* in a short notation titled, "The Success of the Experiment of Transfusing the Blood of One Animal into Another."[11] The entire notation is as follows:[11]

> This experiment, hitherto look'd upon to be of an almost insurmountable difficulty, hath been of late very successfully perform'd not only at Oxford, by the directions of that expert anatomist Dr. Lower, but also in London, by order of the R. Society, at their publick meeting in Gresham Colledge: the Description of the particulars whereof, and the Method of Operation is referred to the next opportunity.

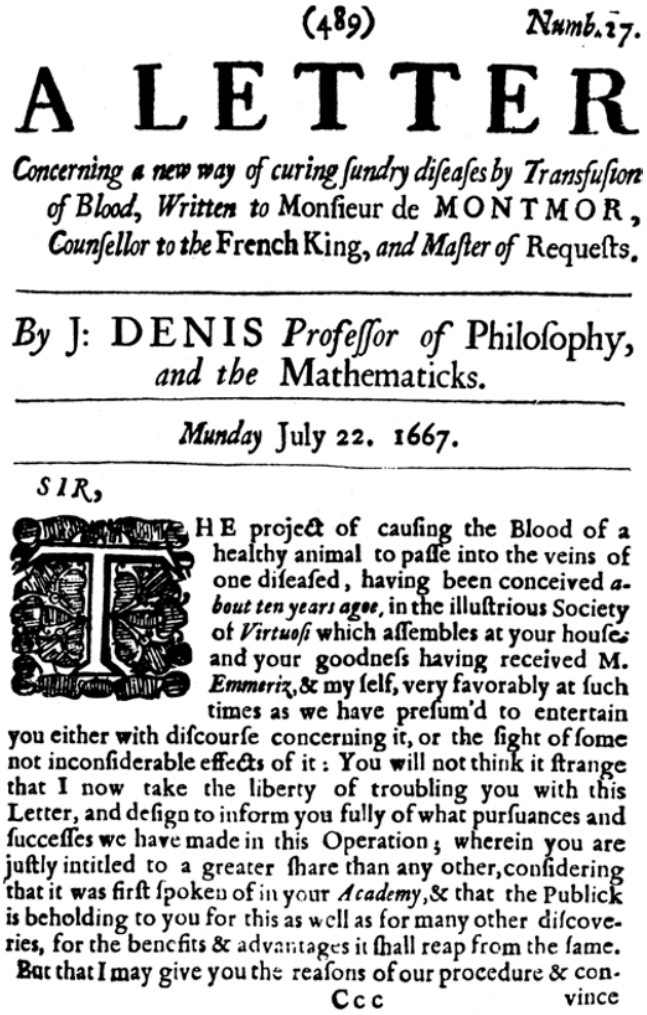
The December 17, 1666, issue of the *Transactions* contained the full description as promised.[12] It was taken from a letter[13] written by Lower to Robert Boyle on July 6, 1666, in which Lower described direct transfusion from the carotid artery of one dog to the jugular vein of another. After describing the insertion of quills into the blood vessels of the donor and recipient dogs, Lower wrote:[13]

> When you have done this you may lay the dogs on their side and fasten them densely together as best you may to insure the connection of the two quills. Quickly tighten the noose around the neck of the receiving animal as in venasection, or at all events compress the vein on the opposite side of the neck with your finger, then take out the stopper and open the upper jugular quill so that while the foreign blood is flowing into the lower quill, the animal's own blood flows out from the upper into suitable receptacles—until at last the second animal, amid howls, faintings, and spasms, finally loses its life together with its vital fluid.
>
> When the tragedy is over, take both quills out of the jugular vein of the surviving animal, tie tightly with the former slipknots, and divide the vein. After the vessel has been divided, sew up the skin, slacken the cords binding the dog, and let it jump down from the table. It shakes itself a little, as though aroused from sleep, and runs away lively and strong, more active and vigorous perhaps, with the blood of its fellow than its own.

These studies inevitably led to the transfusion of animal blood to humans. In England, this occurred on November 23, 1667, when Lower and Edmund King transfused sheep blood into a man named Arthur Coga.[14] Described by Samuel Pepys as "a little frantic," Coga was paid 20 shillings to accept this transfusion, with the expectation that it might have a beneficial "cooling" effect. One week later, Coga appeared before the Society and claimed to be a new man, although Pepys concluded he was "cracked a little in the head."[13] However, this was not the first transfusion performed in a human. The credit for that accomplishment belongs to Jean-Baptiste Denis (1635–1704), who had performed the first human transfusion several months earlier in Paris.

The first animal-to-human transfusion

The founding of the Royal Society in London in 1662 was followed in 1666 by the establishment of the Academie des Sciences in Paris under the patronage of King Louis XIV. The new Academie reviewed the English reports on transfusion with great interest. Denis probably read of Lower's experiments in the *Journal des Savants* on January 31, 1667, and he began his own studies approximately one month later.[15,16] The first human transfusion was



(489) Numb. 27.

A LETTER

Concerning a new way of curing ſundry diſeaſes by Tranſfuſion of Blood, Written to Monſieur de MONTMOR, *Counſellor to the* French King, *and Maſter of* Requeſts.

By J: DENIS *Profeſſor of* Philoſophy, *and the* Mathematicks.

Munday July 22. 1667.

SIR,

THE project of cauſing the Blood of a healthy animal to paſſe into the veins of one diſeaſed, having been conceived *about ten years agoe*, in the illuſtrious Society of *Virtuoſi* which aſſembles at your houſe; and your goodneſs having received M. *Emmeriz*, & my ſelf, very favorably at ſuch times as we have preſum'd to entertain you either with diſcourſe concerning it, or the ſight of ſome not inconſiderable effects of it: You will not think it ſtrange that I now take the liberty of troubling you with this Letter, and deſign to inform you fully of what purſuances and ſucceſſes we have made in this Operation; wherein you are juſtly intitled to a greater ſhare than any other, conſidering that it was firſt ſpoken of in your *Academy*, & that the Publick is beholding to you for this as well as for many other diſcoveries, for the benefits & advantages it ſhall reap from the ſame. But that I may give you the reaſons of our procedure & con-

Ccc vince

Figure 1.1 The first human transfusion. Source: Denis (1967).[17] Figure 01, p 01 / With permission of The Royal Society.

then performed on June 15, 1667, when Denis administered the blood of a lamb to a 15-year-old boy (Figure 1.1).

Although discovery of the circulation had suggested the idea of transfusion, indications for the procedure remained uninformed. Transfusion was still thought to alter behavior and possibly achieve rejuvenation. The blood of young dogs made old dogs seem frisky; the blood of lions was proposed as a cure for cowardice; and, five months later, Arthur Coga would receive a transfusion of sheep blood because of its presumed "cooling" effect. Denis used animal blood for transfusion because he thought it was "less full of impurities":[17]

> Sadness, Envy, Anger, Melancholy, Disquiet and generally all the Passions, are as so many causes which trouble the life of man, and corrupt the whole substance of the blood: Whereas the life of Brutes is much more regular, and less subject to all these miseries.

It is thus ironic that the symptoms of the first transfusion recipient may have been explained in part by profound anemia; the single transfusion of lamb blood may have produced temporary amelioration owing to increased oxygen transport. Denis described the case as follows:[17]

> On the 15 of this Moneth, we hapned upon a Youth aged between 15 and 16 years, who had for above two moneths bin tormented with a contumacious and violent fever, which obliged his Physitians to bleed him 20 times, in order to asswage the excessive heat.

> Before this disease, he was not observed to be of a lumpish dull spirit, his memory was happy enough, and he seem'd cheerful and nimble enough in body; but since the violence of this fever, his wit seem'd wholly sunk, his memory perfectly lost, and his body so heavy and drowsie that he was not fit for anything. I beheld him fall asleep as he sate at dinner, as he was eating his Breakfast, and in all occurrences where men seem most unlikely to sleep. If he went to bed at nine of the clock in the Evening, he needed to be wakened several times before he could be got to rise by nine the next morning, and he pass'd the rest of the day in an incredible stupidity.
>
> I attributed all these changes to the great evacuations of blood, the Physitians had been oblig'd to make for saving his life.

Three ounces of the boy's blood were exchanged for 9 ounces of lamb arterial blood. Several hours later the boy arose, and "for the rest of the day, he spent it with much more liveliness than ordinary." Thus, the first human transfusion, which was heterologous, was accomplished without any evident unfavorable effect.

This report stimulated a firestorm of controversy over priority of discovery.[18,19] The letter by Denis was published in the *Transactions* on July 22, 1667, while the editor, Henry Oldenburg, was imprisoned in the Tower of London. Oldenburg, following some critical comments concerning the Anglo-Dutch War then in progress (1665–1667), had been arrested under a warrant issued on June 20, 1667. After his release two months later, Oldenburg returned to his editorial post and found the letter published in his absence. He took offense at Denis's opening statement, which claimed that the French had conceived of transfusion "about ten years ago, in the illustrious Society of Virtuosi" (Figure 1.1). This seemed to deny the English contributions to the field. Oldenburg cited these omissions in an issue of the *Transactions* published September 23, 1667, "for the Months of July, August, and September." By numbering this issue 27 and beginning pagination with 489, Oldenburg attempted to suppress the letter by Denis.[18] However, as is evident, this did not ultimately succeed. Nonetheless, subsequent events created even greater difficulties for Denis.

Although the first two subjects who underwent transfusion by Denis were not adversely affected, the third and fourth recipients died. The death of the third subject was easily attributable to other causes. However, the fourth case initiated a sequence of events that put an end to transfusion for 150 years.

Anthony du Mauroy was a 34-year-old man who suffered from intermittent bouts of maniacal behavior. On December 19, 1667, Denis and his assistant Paul Emmerez removed 10 ounces of the man's blood and replaced it with 5 or 6 ounces of blood from the femoral artery of a calf. Failing to note any apparent improvement, they repeated the transfusion 2 days later. After the second transfusion, du Mauroy experienced a classic transfusion reaction:[20]

> His pulse rose presently, and soon after we observ'd a plentiful sweat over all his face. His pulse varied extremely at this instant, and he complain'd of great pains in his kidneys and that he was not well in his stomach.

Du Mauroy fell asleep at about 10 o'clock in the evening. He awoke the following morning and "made a great glass full of urine, of a color as black, as if it had been mixed with the soot of chimneys."[20] Two months later, the patient again became maniacal, and his wife again sought transfusion therapy. Denis was reluctant but finally gave in to her urgings. However, the transfusion could not be accomplished, and du Mauroy died the next evening.

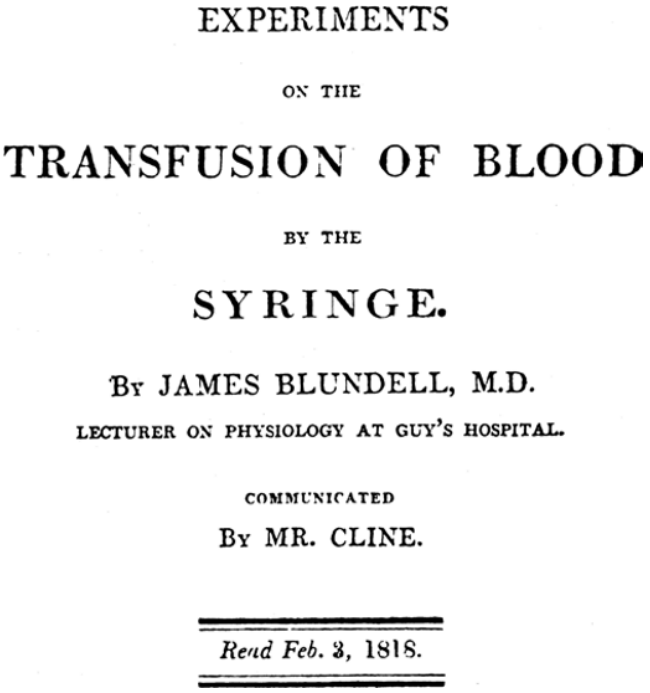
The physicians of Paris strongly disapproved of the experiments in transfusion. Three of them approached du Mauroy's widow and encouraged her to lodge a malpractice complaint against Denis. She instead went to Denis and attempted to extort money from him in return for her silence. Denis refused and filed a complaint before the Lieutenant in Criminal Causes. During the subsequent hearing, evidence was introduced to indicate that Madame du Mauroy had poisoned her husband with arsenic. In a judgment handed down at the Chatelet in Paris on April 17, 1668, Denis was exonerated, and the woman was held for trial. The court also stipulated "that for the future no transfusion should be made upon any human body but by the approbation of the Physicians of the Parisian Faculty."[21] At this point, transfusion research went into decline, and within 10 years it was prohibited in both France and England.

The beginnings of modern transfusion

After the edict that ended transfusion in the seventeenth century, the technique lay dormant for 150 years. Stimulated by earlier experiments by Leacock, transfusion was "resuscitated" and placed on a rational basis by James Blundell (1790–1877), a London obstetrician who had received his medical degree from the University of Edinburgh.[22] Soon after graduation, Blundell accepted a post in physiology and midwifery at Guy's Hospital. It was there that he began the experiments on transfusion that led to its rebirth. The frequency of postpartum hemorrhage and death troubled Blundell. In 1818, he wrote:[23]

> A few months ago I was requested to visit a woman who was sinking under uterine hemorrhage. . . . Her fate was decided, and notwithstanding every exertion of the medical attendants, she died in the course of two hours.
>
> Reflecting afterwards on this melancholy scene . . . I could not forbear considering, that the patient might very probably have been saved by transfusion; and that . . . the vessels might have been replenished by means of the syringe with facility and prompitude.

This opening statement introduced Blundell's epoch-making study titled "Experiments on the Transfusion of Blood by the Syringe"[23] (see Figure 1.2). Blundell described in detail a series



EXPERIMENTS

ON THE

TRANSFUSION OF BLOOD

BY THE

SYRINGE.

By JAMES BLUNDELL, M.D.

LECTURER ON PHYSIOLOGY AT GUY'S HOSPITAL.

COMMUNICATED

By MR. CLINE.

Read Feb. 3, 1818.

Figure 1.2 The beginnings of modern transfusion. Source: Blundell (1818).[23] Figure 01, p 01 / With permission of The Royal Society of Medicine.

of animal experiments. He demonstrated that a syringe could be used effectively to perform transfusion, that the lethal effects of arterial exsanguination could be reversed by the transfusion of either venous or arterial blood, and that the injection of 5 drams (20 cc) of air into the veins of a small dog was not fatal but transfusion across species ultimately was lethal to the recipient.[23] Thus, Blundell was the first to clearly state that only human blood should be used for human transfusion. The latter conclusion was confirmed in France by Dumas and Prevost, who demonstrated that the infusion of heterologous blood into an exsanguinated animal produced only temporary improvement and was followed by death within six days.[24] These scientific studies provided the basis for Blundell's subsequent efforts in clinical transfusion.

The first well-documented transfusion with human blood took place on September 26, 1818.[25] The patient was an extremely emaciated man in his mid-thirties who had pyloric obstruction caused by carcinoma. He received 12 to 14 ounces of blood in the course of 30 or 40 minutes. Despite initial apparent improvement, the patient died two days later. Transfusion in the treatment of women with postpartum hemorrhage was more successful. In all, Blundell performed 10 transfusions, of which 5 were successful. Three of the unsuccessful transfusions were performed on moribund patients, the fourth was performed on a patient with puerperal sepsis, and the fifth was performed on the aforementioned patient with terminal carcinoma. Four of the successful transfusions were given for postpartum hemorrhage, and the fifth was administered to a boy who bled after amputation.[22] Blundell also devised various instruments for the performance of transfusion. They included an "impellor," which collected blood in a warmed cup and "impelled" the blood into the recipient via an attached syringe, and a "gravitator"[26] (Figure 1.3), which received blood and delivered it by gravity through a long vertical cannula.

The writings of Blundell provided evidence against the use of animal blood in humans and established rational indications for transfusion. However, the gravitator (Figure 1.3) graphically demonstrated the technical problems that remained to be solved. Blood from the donor, typically the patient's husband, flowed into a funnel-like device and down a flexible cannula into the patient's vein "with as little exposure as possible to air, cold, and inanimate surface."[25] The amount of blood transfused was estimated from the amount spilled into the apparatus by the donor. In this clinical atmosphere, charged with apprehension and anxiety, the amount of blood issuing from a donor easily could be overstated. Clotting within the apparatus then ensured that only a portion of that blood actually reached the patient. Thus, the amount of blood actually transfused may have been seriously overestimated. This may explain the apparent absence of transfusion reactions. Alternatively, reactions may have been unrecognized. Patients who underwent transfusion frequently were agonal. As Blundell stated, "It seems right, as the operation now stands, to confine transfusion to the first class of cases only, namely, those in which there seems to be no hope for the patient, unless blood can be thrown into the veins."[26] Under these circumstances, "symptoms" associated with an "unsuccessful" transfusion might be ascribed to the agonal state rather than the transfusion itself. For a time, the problem of coagulation during transfusion was circumvented by the use of defibrinated blood. This undoubtedly increased the amount of blood actually transfused. However, there were numerous deaths. Interestingly, these deaths were attributed to intravascular coagulation when in actuality they were probably fatal hemolytic reactions caused by the infusion of incompatible blood.[27]

Vol. II.] LONDON, SATURDAY, JUNE 13. [1828-9.

OBSERVATIONS
ON
TRANSFUSION OF BLOOD.

By Dr. Blundell.

*With a Description of his Gravitator.**

States of the body really requiring the infusion of blood into the veins are probably rare; yet we sometimes meet with cases in which the patient must die unless such operation can be performed; and still more frequently with cases which seem to require a supply of blood, in order to prevent the ill health which usually arises from large losses of the vital fluid, even when they do not prove fatal.

* The instrument is manufactured by Messrs. Maw, 35, Aldermanbury.

In the present state of our knowledge respecting the operation, although it has not been clearly shown to have proved fatal in any one instance, yet not to mention possible, though unknown risks, inflammation of the arm has certainly been produced by it on one or two occasions; and therefore it seems right, as the operation now stands, to confine transfusion to the first class of cases only, namely, those in which there seems to be no hope for the patient, unless blood can be thrown into the veins.

The object of the Gravitator is, to give help in this last extremity, by transmitting the blood in a regulated stream from one individual to another, with as little exposure as may be to air, cold, and inanimate surface; ordinary venesection being the only operation performed on the person who emits the blood; and the insertion of a small tube into the vein usually laid open in bleeding, being all the operation which it is necessary to execute on the person who receives it.

The following plate represents the whole apparatus connected for use and in action:—

Tab. 1.

No. 302. Y

Figure 1.3 Blundell's gravitator. Source: Blundell (1828).[26] With permission of Jeremy Norman & Co., Inc.

Transfusion at the end of the nineteenth century, therefore, was neither safe nor efficient. The following description, written in 1884, illustrates this point:[28]

> Students, with smiling faces, are rapidly leaving the theatre of one of our metropolitan hospitals. The most brilliant operator of the day has just performed immediate transfusion with the greatest success. By means of a very beautiful instrument, the most complex and ingenious that modern science has yet produced, a skilful surgeon has transfused half a pint, or perhaps a pint, of blood from a healthy individual to a fellow creature profoundly collapsed from the effects of severe hemorrhage. Some little difficulty was experienced prior to the operation, as one of the many stop-cocks of the transfusion apparatus was found to work stiffly; but this error was quickly rectified by a mechanic in attendance. Towards the close of the operation the blood-donor, a powerful and heavy young man, swooned. Two porters carried him on a stretcher into an adjoining room.

In the latter half of the nineteenth century, there were many attempts to render transfusion a more predictable and less arduous procedure. In 1869, Braxton-Hicks,[29] using blood anticoagulated with phosphate solutions, performed a number of transfusions on women with obstetric bleeding. Many of the