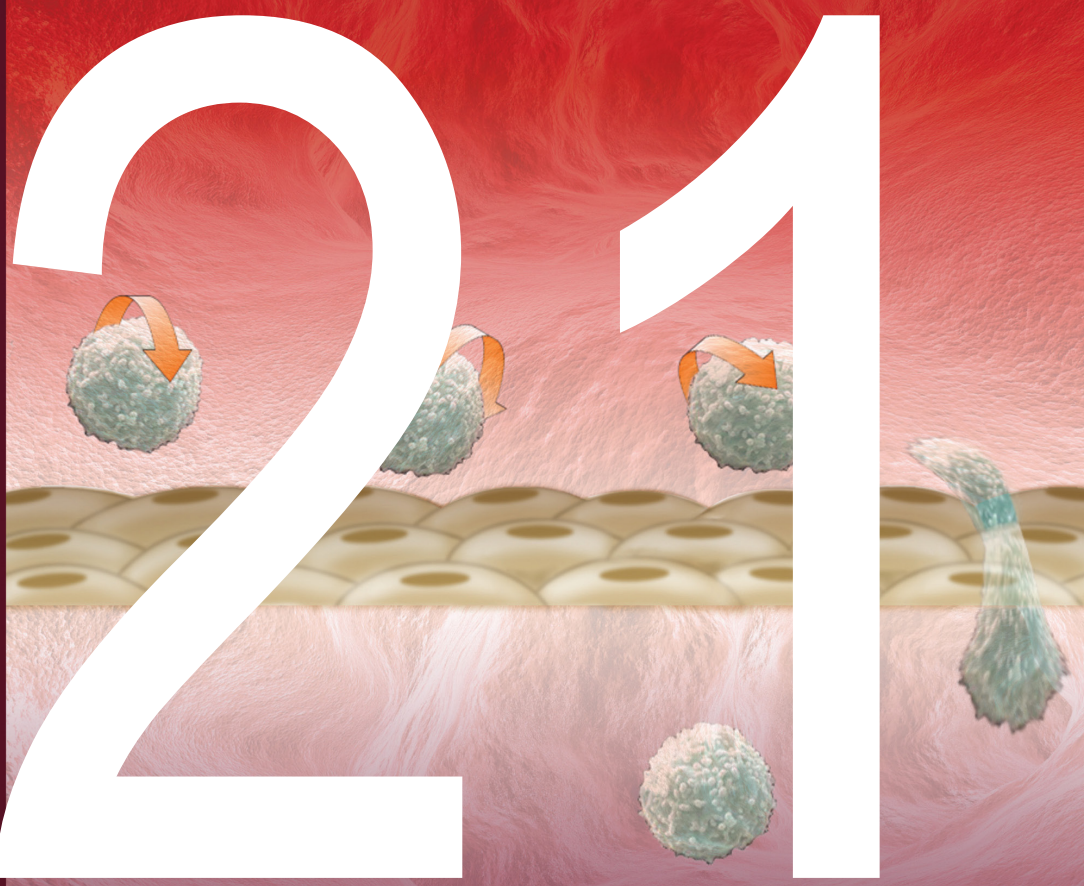
Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists



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Mechanisms of Vascular Disease

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A Reference Book for Vascular Specialists

Robert Fitridge
The University of Adelaide, The Queen Elizabeth Hospital, Woodville, Australia
Matthew Thompson
St George's Hospital Medical School, London, UK

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List of Contributors

David G Armstrong
The University of Arizona
Southern Arizona Limb Salvage Alliance
Tucson, AZ
USA

Vishwanath Biradar
Intensive Care Unit
The Queen Elizabeth Hospital
Woodville, SA
Australia

Matthew Bown
Department of Vascular Surgery
University of Leicester
Leicester
UK

Andrew W Bradbury
University Department of Vascular Surgery
Birmingham Heartlands Hospital
Birmingham
UK

Edward Choke
Department of Vascular Surgery
University of Leicester
Leicester
UK

Gillian Cockerill
Department of Clinical Sciences
St George's Hospital Medical School
London
UK

Prue Cowled
Department of Surgery
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Helen Daly
Royal Perth Hospital
Perth, WA
Australia

Mital Desai
University Department of Vascular Surgery
Royal Free Hospital
University College
London
UK

Robert F Diegelmann
Department of Biochemistry
Medical College of Virginia
Richmond, VA
USA

Timothy K Fisher
Rashid Centre for Diabetes and Research
Sheikh Khalifa Hospital
Ajmon
UAE

Robert A Fitridge
Department of Surgery
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Gail Gillespie
Royal Perth Hospital
Perth, WA
Australia

Jonathan Golledge
Vascular Biology Unit
School of Medicine & Dentistry
James Cook University
Townsville, QLD
Australia

George Hamilton
University Department of Vascular Surgery
Royal Free Hospital
University College
London
UK

Mark Hamilton
Department of Surgery
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Robert J Hinchliffe
St George's Vascular Institiute
St George's Hospital
London
UK

Richard D Kenagy
Department of Surgery
University of Washington
Seattle, WA
USA

Paul Kerr
Department of Pharmacology
University of Alberta
Alberta
Canada

Michael MD Lawrence-Brown
Curtin Health Innovation Research Institute
Curtin University
Perth, WA
Australia

Brian Lepow
The University of Arizona
Department of Surgery
Southern Arizona Limb Salvage Alliance
Tucson, AZ
USA

Kurt Liffman
CSIRO Material Science & Engineering and School of Mathematical Sciences
Monash University
Melbourne, Vic
Australia

Ian Loftus
Department of Vascular Surgery
St George's Hospital
London
UK

Mark J McCarthy
Department of Surgery and Cardiovascular Sciences
University of Leicester
Leicester
UK

Greg S McMahon
Department of Surgery and Cardiovascular Sciences
University of Leicester
Leicester
UK

Simon McRae
Adult Haemophilia Treatment Centre
SA Pathology
Adelaide, SA
Australia

Joseph L Mills
The University of Arizona
Southern Arizona Limb Salvage Alliance
Tucson, AZ
USA

Lyle Moldawer
Department of Surgery
University of Florida
Gainesville, FL
USA

John L Moran
Faculty of Health Sciences
University of Adelaide
The Queen Elizabeth Hospital
Woodville, SA
Australia

Stephen Nicholls
The Heart and Vascular Institute
Cleveland Clinic
Cleveland, OH
USA

Ian M Nordon
St George's Vascular Institiute
St George's Hospital
London
UK

Paul E Norman
School of Surgery
University of WA
Fremantle, WA
Australia

Karlheinz Peter
Baker IDI Heart & Diabetes Institute
Melbourne, Vic
Australia

Frances Plane
Department of Pharmacology
University of Alberta
Alberta
Canada

Janet T Powell
Imperial College
London
UK

Sandeep Prabhu
Baker IDI Heart & Diabetes Institute
Alfred Hospital
Melbourne, Vic
Australia

Rishi Puri
The Heart and Vascular Institute
Cleveland Clinic
Cleveland, OH
USA

Stephan A Schug
Royal Perth Hospital
Perth, WA
Australia

Gregory S Schultz
Department of Obstetrics and Gynaecology
University of Florida
Gainesville, FL
USA

Rahul Sharma
Baker IDI Heart & Diabetes Institute
Alfred Hospital
Melbourne, Vic
Australia

Guo-Ping Shi
Department of Cardiovascular Medicine
Brigham & Women's Hospital
Harvard Medical School
Boston, MA
USA

Michael Stacey
University Department of Surgery
Fremantle Hospital
Fremantle, WA
Australia

Ilija D Sutalo
CSIRO Material Science & Engineering
and Curtin Health Innovation
Research Instutute
Curtin University
Highett, Vic

Raymond Tam
Department of Pharmacology
University of Alberta
Alberta
Canada

Matthew Thompson
St Georges Hospital Medical School
London
UK

Martin Veller
Department of Surgery
University of Witwatersrand
Johannesburg
South Africa

Mauro Vicaretti
Department of Vascular Surgery
Westmead Hospital
Westmead, NSW
Australia

Matt Waltham
Academic Department of Surgery
St Thomas' Hospital
London
UK

Matthew L White
Vascular and Endovascular Surgery
University of Arizona
Tucson, AZ
USA

David P Wilson
School of Medical Sciences
Discipline of Physiology
University of Adelaide
Adelaide SA
Australia

Qingbo Xu
Department of Cardiology
Kings College
University of London
UK

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Abbreviation List

a1-PI	a1-protease inhibitor
5-HT	5-Hydroxytryptamine/Serotonin
AAA	Abdominal aortic aneurysm
AAS	Acute aortic syndrome
AAV	Adeno-associated viruses
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ACS	Abdominal compartment syndrome
ACTH	Adrenocorticotropic hormone
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
ADP	Adenosine diphosphate
AIDS	Acquired immune deficiency syndrome
ALI	Acute lung injury
AMP	Adenosine monophosphate
AMPA	α-amino-3 hydroxy-5-methylisoxazole
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
AOD	Aortic occlusive disease
AP1	Activated protein 1
APC	Activated protein C
APC	Antigen presenting cell
APLAS	Antiphospholipid antibody syndrome
ApoAI	Apolipoprotein AI
ApoE	Apolipoprotein E
APS	Antiphospholipid antibody syndrome
APTT	Activated partial thromboplastin time

ARDS	Acute respiratory distress syndrome
AT	Antithrombin
ATP	Adenosine triphosphate
AVP	Ambulatory venous thrombosis
β2-GPI	β2-glycoprotein Ib
bFGF	Basic fibroblast growth factor
BKCa	Large conductance calcium activated potassium channel
BMPs	Bone morphogenetic proteins
BMS	Bare metal stent
CAD	Coronary artery disease
CaM	Calmodulin
CAM	Cell adhesion molecule
cAMP	Cyclic adenosine monophosphate
CCK	Cholecystokinin
cGMP	Cyclic guanine monophosphate
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
CEA	Carotid endarterectomy
CETP	Cholesteryl ester transfer protein
CFD	Computational fluid dynamics
CG	Cationized gelatin
CGRP	Calcitonic gene regulated peptide
CHD	Coronary heart disease
CI	Confidence interval
CIMT	Carotid intimal-media thickness
c-JNK	c-Jun N-terminal kinase
CK-MB	Creatinine kinase (Myocardial specific)
CNCP	Chronic noncancer pain
cNOS	Constitutive nitric oxygen synthase enzyme
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CROW	Charcot restraint orthotic walker
CRRT	Continuous renal replacement therapy

CRP	C-reactive protein
CRPS	Complex regional pain syndromes
CT	Computational tomography
CTA	Computed tomographic angiography
CTD	Connective tissue disorders
CTGF	Connective tissue growth factor
CYP	Cytochrome P450
CVD	Cardiovascular disease
CVI	Chronic venous insufficiency
DAG	Diacylglycerol
DES	Drug-eluting stent
DRG	Dorsal root ganglion
DNA	Deoxyribonucleic acid
DSA	Digital subtraction arteriography
DTS	Dense tubular system
DVT	Deep vein thrombosis
EC	Endothelial cell
ECM	Extracellular matrix
EDCF	Endothelium-derived contracting factor
EDH	Endothelium-dependent hyperpolarisation
EDS	Ehlers-Danlos syndrome
EET	Epoxyeicosatrienoic acids
ELAM-1	Endothelial-leukocyte adhesion molecule-1
ELG	Endoluminal grafts
ELISA	Enzyme linked immunosorbent assay
E_K	Equilibrium potential
E_M	Membrane potential
eNOS	Endothelial nitric oxide synthase enzyme
EPC	Endothelial progenitor cells
EPCR	Endothelial protein C receptor
ePTFE	Expanded polytetrafluoroethylene
ERK	Extracellular signal-regulated kinase
ESR	Erythrocyte sedimentation rate

ET	Essential thrombocytosis
ET-1	Endothelin 1
EVAR	Endovascular aortic aneurysm repair
EVLA	Endovenous LASER ablation
FDA	Food and drug administration
FDPs	Fibrin degradation products (soluble)
FGF	Fibroblast growth factor
FGF-2	Fibroblast growth factor 2
FMN	Flavin mononucleotide
FVL	Factor V Leiden
GABA	Gamma-aminobutyric acid
GABA B	Gamma-aminobutyric acid subtype B
G-CSF	Granulocyte colony stimulating factor
GMCSF	Granulocyte-macrophage colony stimulating factor
GP	Glycoprotein
GPCR	G-protein coupled receptor
GSV	Great saphenous vein
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HIF	Hypoxia inducible factor
HIT	Heparin induced thrombocytopenia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG Co-A	Hydroxymethylglutaryl coenzyme-A
HMW	High molecular weight
HPETE	Hydroperoxyeicosatetraenoic acid
HETE	Hydroxyeicosatetraenoic acids
HR	Hazard ratio
hsCRP	High-sensitive C-reactive protein
HSP	Heat shock protein
HUV	Human umbilical vein
IAH	Intra-abdominal hypertension

IAP	Intra-abdominal pressure
IAPP	Intra-abdominal perfusion pressure
ICAM-1	Inter-cellular adhesion molecule-1
ICAM-2	Inter-cellular adhesion molecule-2
ICP	Intra-compartmental pressure
ICU	Intensive care unit
IFN	Interferon
IGF-1	Insulin-like growth factor-1
IHD	Ischemic heart disease
IL	Interleukin
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL1-β	Interleukin-1 beta
IL-6	Interleukin-6
IL-8	Interleukin-8
ILT	Intraluminal thrombus
IKCa	Intermediate conductance calcium-activated potassium channels
IMH	Intramural haematoma
IMP	Inosine monophosphate
iNOS	Inducible nitric oxide synthase enzyme
IP(3)	1,4,5-inositol triphosphate
IRI	Ischemia reperfusion injury
IVIG	Intravenous pooled immunoglobulin
IVUS	Intravascular ultrasound
KGF	Keratinocyte growth factor
KGF-2	Keratinocyte growth factor-2
LAP	Latency associated peptide
LCS	Limb compartment syndrome
LDL	Low density lipoprotein
LDS	Loeys-Dietz syndrome
LLC	Large latent complex
LEC	Lymphatic endothelial cells

LFA-1	Lymphocyte function-associated antigen-1
LO	Lipoxygenase
LOX	Lysyl oxidase
LOPS	Loss of protective sensation
LPA	Lysophosphatidic acid
LPS	Lipopolysaccharide
LTA	Lipoteichoic acid
LTGFBP	Latent TGF binding protein
MAC-1	Macrophage-1 antigen
MAPK	Mitogen activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage-colony stimulating factor
MFS	Marfan syndrome
MHC	Major histocompatibility
MI	Myocardial infarction
MIP-1	Macrophage inflammatory protein-1
MLC_{20}	Myosin light $chain_{20}$
MLCK	Myosin light chain kinase
MLCP	Myosin light chain phosphatase
MMP	Matrix metalloproteinase
MODS	Multiple organ dysfunction syndrome
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MRSA	Methicillin resistant *Staphylococcus aureus*
MRSE	Methicillin resistant *Staphylococcus epidermidis*
MRTA	Magnetic resonance tomographic angiography
MTHFR	Methylenetetrahydrofolate reductase
MT-MMP	Membrane-type MMP
MVPS	Mitral valve prolapse syndrome
NADPH	Nicotinamide adenine dinucleotide phosphate
NGF	Nerve growth factor

NFκB	Nuclear factor kappa B
NiTi	Nitinol
NJP	Non-junctional perforators
NMDA	N-methyl-D-aspartate
NNH	Number needed to harm
NNT	Number needed to treat
NO	Nitric oxide
NOS	Nitric oxide synthase enzyme
NSAID	Non-steroidal anti-inflammatory drug
NV	Neovascularisation
OCP	Oestrogen/progesterone contraceptive pill
OPN	Osteopontin
OPG	Osteoprotegerin
OR	Odds ratio
OxLDL	Oxidised low density lipoprotein
PAD	Peripheral arterial disease
PAF	Platelet activating factor
PAI	Plasminogen activator inhibitor
PAI-1	Plasminogen activator inhibitor-1
PAR	Protease activated receptor
PAR-1	Protease activated receptor-1
PAR-4	Protease activated receptor-4
PAU	Penetrating aortic ulcer
PC	Protein C
PCA	Poly (carbonate-urea) urethane
PCI	Percutaneous coronary intervention (angioplasty)
PCWP	Pulmonary capillary wedge pressure
PDGF	Platelet-derived growth factor
PDGFβ	Platelet-derived growth factor-β
PDS	Polydioxanone
PECAM-1	Platelet-endothelial cell adhesion molecule-1
PEDF	Pigment epithelium-derived factor
PES	Paclitaxel-eluting stent

PET	Positron emission tomography
PF4	Platelet factor 4
PGI_2	Prostacyclin
PGG_2	Prostaglandin G_2
PGH_2	Prostaglandin H_2
$PGEI_2/PGI_2$	Prostaglandin I_2
PGN	Peptidoglycan
PHN	Postherpetic neuropathy
PHZ	Para-anastomotic hyper-compliant zone
PI3K	Phosphatidylinositol 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PLC	Phospholipase C
PLOD	Procollagen lysyl hydroxylase
PMCA	Plasma membrane Ca^{2+} APTases
PMN	Polymorphonuclear leukocyte
POSS	Polyhedral oligomeric silsesquioxanes
PPAR	Peroxisomal proliferation activating receptor
PPI	Proton pump inhibitor
PRV	Polycythaemia rubra vera
PS	Protein S
PSGL-1	P-selectin glycoprotein ligand-1
PT	Prothombin time
PTCA	Percutaneous coronary angioplasty
PTFE	Polytetrafluoroethylene
PTS	Post-thrombotic syndrome
PUFA	Polyunsaturated fatty acid
PVI	Primary valvular incompetence
rAAA	Ruptured AAA
Rac	Ras activated cell adhesion molecule
RANTES	Regulated upon activation, normal T cell expressed and secreted
RAS	Renin angiotensin system
RCT	Randomised controlled trial

RF	Rheumatoid factor
RFA	Radiofrequency ablation
rhAPC	Recombinant human activated protein C
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RR	Relative risk
RSD	Reflex sympathetic dystrophy
S1P	Sphingosine-1-phosphate
SAPK	Stress-activated protein kinase
SCF	Stem cell factor
SCS	Spinal cord stimulation
ScvO2	Superior vena cava venous oxygen saturation
SDF-1	Stromal-cell-derived factor-1
SERCA	Sarco/endoplasmic reticulum CaATPases
SEP	Serum elastin peptides
SES	Sirolimus-eluting stent
SEPS	Subfascial endoscopic perforator surgery
SFA	Superficial femoral artery
SFJ	Sapheno-femoral junction
SIRS	Systemic inflammatory response syndrome
SKCa	Small conductance calcium-activated potassium channels
SLE	Systemic lupus erythematosus
SMA	Smooth muscle alpha actin
SMC	Smooth muscle cell
SMP	Sympathetically maintained pain
SNARE	Soluble N-ethylmaleimide-sensitive factor activating protein receptors
SNP	Single nucleotide polymorphisms
SNRI	Serotonin/Noradrenaline reuptake inhibitors
SPJ	Sapheno-popliteal junction
SPP	Skin perfusion pressure
SR	Sarcoplasmic reticulum
SSRIs	Selective serotonin re-uptake inhibitors
SSV	Small saphenous vein

SVT	Superficial thrombophlebitis
STIM1	Stromal interacting molecule 1
TαCE	TNFα converting enzyme
TAAD	Thoracic aortic aneurysm disease
TAD	Thoracic aortic dissection
TAFI	Thrombin-activatable fibrinolysis inhibitor
Tc-99 MDP	Technetium-99 methylene diphosphonate
TCA	Tricyclic antidepressant
TCC	Total contact cast
TCR	T-cell receptor
TENS	Transcutaneous electrical nerve stimulation
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TGF	Transforming growth factor
TGF-α	Transforming growth factor-alpha
TGF-β	Transforming growth factor-beta
TGL	Triglycerides
Th	T helper
TIA	Transient ischemic attack
TIMP	Tissue inhibitors of metalloproteinase
TLR	Toll-like receptors
TNF	Tumour necrosis factor
TNF-α	Tumour necrosis factor-alpha
tPA	Tissue-type plasminogen activator
TRP	Transient receptor potential
TRPC	Transmembrane receptor potential canonical
TRPV1	Transmembrane receptor potential Vanilloid-type
TXA2	Thromboxane A2
uPA	Urokinase
UT	University of Texas
VCAM	Vascular cell adhesion molecule
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

VEGF-R	Vascular endothelial growth factor receptor
VIP	Vasoactive intestinal peptide
VLA-1	Very late activating antigen-1
VOCC	Voltage operated calcium channels
VPT	Vibratory perception threshold
VSMC	Vascular smooth muscle cells
VTE	Venous thromboembolism
VV	Varicose veins
vWF	von Willebrand factor
XO	Xanthine oxidase

21 • Post-amputation Pain

STEPHAN A. SCHUG, GAIL GILLESPIE

School of Medicine and Pharmacology, University of Western Australia, Royal Perth Hospital, Perth, WA

INTRODUCTION

The phenomenon of pain in a missing limb has puzzled patients, doctors and the lay public for centuries. In the 16th Century the French military surgeon Ambroise Paré published a medical description of the enigmatic affliction, while in the 17th century the great philosopher Rene Descartes looked at its potential pathophysiology. The most famous 'first' description of the condition is attributed to the great neurologist Charles Bell,[1] but it was only in the later part of 19th Century, that the US military surgeon Silas Weir Mitchell introduced the term 'phantom limb': '*There is something almost tragical, something ghastly, in the notion of these thousands of spirit limbs, haunting as many good soldiers, and every now and then tormenting them . . .*'

We now know that post-amputation syndromes can occur with any amputated body part apart from limbs e.g. breast, tongue, teeth, genitalia and even inner organs such as the rectum.[2-4]

CLASSIFICATION AND INCIDENCE OF POST-AMPUTATION PAIN SYNDROMES

Following amputation (or deafferentiation injury such as brachial plexus avulsion) a number of phenomena can develop, which require differentiation.

Stump Pain

Stump pain is pain localized to the site of amputation. Stump pain can be acute (usually nociceptive) or chronic (usually neuropathic). Stump pain is most common in the immediate post-operative period.[5] The overall incidence of chronic stump pain is in the range of 45%.[6] The incidence of early stump pain is increased by the presence of severe pre-amputation pain[7] and severe acute stump pain.[8] The cause is unclear but probably multifactorial. Stump pain is problematic and can interfere with prosthesis use.

Phantom Sensation

Phantom sensation is defined as any sensory perception of the missing body part with the exclusion of pain. Almost all patients who have undergone amputation experience such phantom sensations.[9] These sensations range from a vague awareness of the presence of the organ via associated paraesthesia to complete sensation including size, shape, position, temperature and movement.[10] Phantom sensations usually diminish in intensity or size over time, but may persist for a long time. 'Telescoping' of the phantom part can occur with time such that the phantom limb gradually shrinks proximally to approach the stump.[11] Eventually the phantom limb is felt to be within the stump itself.

Phantom Limb Pain

Phantom limb pain (PLP) is defined as any noxious sensory phenomenon of the missing limb or organ. The incidence of phantom limb pain is estimated to be 60–80% after limb amputation.[5,6] The pain is independent of gender, level or side of amputation.[5] There is, however, a lower incidence among children and congenital amputees.[12]

Pain can be immediate or delayed in onset. It is typically intermittent and changes with time. Typical characteristics of phantom limb pain are burning, shooting, crushing, throbbing, cramping, aching, tingling, boring; often the limb is described as being in a hyperextended or otherwise unnatural position. The pain usually occurs in the distal portion of the missing limb.[5] The incidence of pain may be increased if pre-amputation pain was present and may then resemble the pre-amputation pain in character and localisation.[8,13] However, the exact relationship between pre-amputation pain and PLP is not a simple one, especially as patients' pain perceptions alter and may be exaggerated with time.[5] The incidence of phantom pain diminishes with time after amputation, as does the frequency and intensity, being highest immediately following surgery.[5]

It is important to realise, that the terms for noxious syndromes, 'stump pain' and 'phantom limb pain', are subjective descriptive terms that do not make assumptions on differences in pathophysiology. There is, in fact, a strong correlation between phantom pain and stump pain and they may be inter-related phenomena.[14] All three phenomena can co-exist. [7]

PATHOPHYSIOLOGY OF POST-AMPUTATION PAIN SYNDROMES

The pathophysiology of post-amputation pain syndromes is most likely based on a combination of peripheral and central factors, which interplay subsequent to the significant trauma of an amputation.

Peripheral Factors

The following changes occur after peripheral nerve injury such as cutting of a nerve:[15]

1) Sensitization of peripheral nociceptors with a decreased threshold to noxious stimulation;
2) Increased response to supra-threshold stimulation;
3) Spontaneous activity of peripheral receptors due to sensitisation including ectopic pacemaker sites, possibly as a result of the increase in sodium channels, α-adrenergic channels, calcium channels and stretch-activated channels that follows nerve injury;
4) Sensitization of non-nociceptive receptors to nociceptive impulses.

These changes contribute to hyperalgesia and allodynia in the stump; therefore stump

manipulation and revision can worsen pain due to repeated deafferentation injuries. The dorsal root ganglion may also be the site of ectopic neuronal activity subsequent to deafferentiation and thereby contributing to pain syndromes.

Furthermore, regrowth of severed nerves often produces nodules called 'neuromas'. Neuronal activity originating from peripheral neuromas either spontaneously or in response to mechanical, chemical or electrical stimulation, may cause increased sensitivity of the stump to different stimuli.[15]

Other peripheral factors include increased muscle tension in the stump correlated with cramping and spasmodic pain and decreased blood flow to stump correlates with descriptions of phantom pain such as burning or tingling. Low stump temperature correlates with burning pain.

Overall, while physical stimulation of the stump may accentuate phantom limb pain, current evidence suggests that peripheral mechanisms do not cause, but at most modulate or perpetuate phantom limb pain.

Spinal Factors

The combination of increased afferent input from sensitised nerve endings and the dorsal root ganglion may contribute to central sensitisation. The following changes occur in the dorsal horn of the spinal cord after nerve injury:[15]

1) Increased spontaneous activity of dorsal horn neurones
2) Increased response to afferent input
3) After-discharges following repetitive stimulation
4) Expansion of peripheral receptive fields
5) Wind-up (increased neuronal activity in dorsal horn neurons following repetitive C-fibre stimulation), mainly mediated by N-methyl D-aspartate (NMDA) receptors.

These factors play an important role in many chronic pain syndromes, but to which extent these factors are involved in perpetuation of phantom syndromes is currently unclear, although involvement is likely.

Supraspinal Factors

The presence of pain prior to amputation is thought to increase the likelihood of phantom pain.[13] In 1971, Melzack proposed that the painful extremity had created a painful central 'engram'. An engram is the schematic representation of body parts in the CNS caused by consistent sensory input. This engram was thought to persist after amputation causing phantom pain.

On the basis of these observations, the *neuromatrix theory* was proposed by Melzack in 1990.[16] In this theory, the body's physical self is represented by a matrix, a complex network of neurones connecting somatosensory cortex, thalamus and limbic system. This *neuromatrix* is genetically determined and subsequently modulated by sensory input, thereby creating a *neurosignature* for each body part. This neurosignature determines how a body part is consciously perceived; phantom sensations are the result of persistence of the neurosignature after the loss of the limb. The genetic determination of the neurosignature is supported by the observation that children who are born with a missing limb may feel phantom sensations of the missing part.

In this theory, phantom limb pain is the result of abnormal reorganisation in the matrix, either due to a preexisting pain state or the amputation process itself.[16]

By analysing neuromagnetic fields, the group around Flor has been able to show a close correlation between the degree of neuromatrix reorganisation and the development of phantom limb pain;[17] reorganisation

of somatosensory cortex occurs with neighbouring representation zones moving into the deafferented zone.[18] Here it is also of note that many of the sites of amputation that commonly lead to phantom sensation and pain are sites with a relatively large cortical somatosensory representation.

An alternative theory discussed in the literature is the *dynamic reverberation theory.* This originated from the observation that selective stereotactic cortectomies of the corona radiata or focal brain lesions in the parietal cortex, thalamus or cortico-thalamic fibres on the contralateral side have resulted in permanent relief of phantom pain. This led Canavero, in 1994, to the theory that phantom pain and sensation were a result of a localized dynamic reverberation loop between cortex and thalamus. He postulated that this loop could operate with or without sensory activation.[19]

CURRENT PATHOPHYSIOLOGICAL MODEL OF POST-AMPUTATION PAIN SYNDROMES

A comprehensive model incorporating the current state of knowledge has been proposed by Flor et al. It includes peripheral and central factors as relevant contributors to the development and perpetuation of phantom limb pain.[18] In principle, it suggests that somatosensory pain memories and a subsequently altered homuncular representation in the somatosensory cortex are the underlying factors of phantom limb pain, which can be sustained by peripheral factors. In more detail, it assumes that memories of pain established before an amputation are powerful causative contributors to phantom limb pain generation. In analogy to findings in other chronic pain patients, such pain memories increase the representation zone in the primary somatosensory cortex. The changes are then perpetuated after the amputation by selective C-fibre deafferentiation, random input from stump neuromas, abnormal changes in the dorsal root ganglia and the dorsal horn of the spinal cord and sympathetic activation.[20]

PREVENTION OF POST-AMPUTATION PAIN

In view of the immense difficulties in treating phantom limb pain once it is established, considerable efforts have been made to identify techniques to prevent the syndrome. Regrettably, the evidence on none of the methods tried has been conclusive, although overall results of epidural anaesthesia and possibly ketamine administration are promising.

Perioperative Lumbar Epidural Blockade

In 1988, Bach *et al*. demonstrated that lumbar epidural blockade (LEB) with bupivacaine plus morphine, started 72 hours *prior to surgery*, reduced the incidence of phantom limb pain in the first year after surgery.[21] This promising result initiated a number of similar studies; Schug *et al*. investigated the use of pre-emptive lumbar epidural anaesthesia/analgesia preoperatively for 24 hours and postoperatively for 72 hours in a small sample of patients. At an interview one year after amputation, those patients with epidural analgesia had significantly less severe phantom limb pain than those receiving general anaesthesia.[22]

Another study comparing pre-operative and intra-operative analgesia using LEB showed no difference between groups. The duration of pre-operative LEB, however was variable between patients with a median pre-operative infusion of 18 hours.[23] However, this study has been criticised for its quality

of analgesia and the inclusion of pain of any intensity in the results.

More recently, Lambert and colleagues compared pre-operative epidural with perineural analgesia. The LEB was started 24 hours before surgery and continued for three days post-operatively. No difference was found in stump or phantom pain or in phantom sensation at six and 12 months.[24] Although this was a randomised trial, the numbers were small and it is questionable whether the study had sufficient power for phantom pain outcome measurements.

In conclusion, there have been several studies looking at preventive analgesia using LEB. The results are conflicting,[25] however a meta-analysis showed that perioperative epidural analgesia reduced the incidence of severe phantom limb pain with an NNT of 5.8.[26] Overall the results are promising and a protective effect has again been confirmed in a recent audit at our institution.

Peripheral Nerve Blockade

Infusions of local anaesthetics via peripheral nerve sheath catheters, usually inserted by the surgeon during the amputation, are a safe method providing excellent analgesia for the immediate post-operative wound pain. They are, however, of no proven benefit in the prevention of phantom pain or stump pain.[25]

NMDA Antagonists

The use of pre-incision ketamine as pre-emptive analgesia has been described previously in other settings. A small observational study suggests that the incidence of severe phantom limb pain may be reduced with the use of ketamine as a bolus followed by an infusion started prior to skin incision and continued for 72 hours post-operatively.[27] This promising study was small and used historical controls. A randomised controlled trial could not confirm these results, but was underpowered.[28] Epidural ketamine had no preventive effect in an RCT.[29] However, a trial of memantine in combination with regional analgesia showed a preventive effect.[30] Overall, further investigations are justified.

EVALUATION OF THE PATIENT WITH POST-AMPUTATION PAIN SYNDROMES

Phantom sensation requires pre- and post-operative counselling and education but it should not generally pose a clinical problem.

Examination

Examine stump to exclude common causes:

1) Prosthogenic Pain
   a) Due to an improperly fitting prosthesis:
      i) Poor socket fit, cushioning or alignment
   b) Inappropriate suspension resulting in pistoning
   c) Painful adductor roll in the above-knee amputee
   d) Distal residual limb weight-bearing
   e) Poor trim line
2) Neuropathic Pain
   a) Caused by neuroma formation
   b) Test for presence of wind-up by examining for Tinel's sign – shooting pains elicited by repeated tapping over the area
3) Arthrogenic Pain
   a) Pain originating in neighbouring joint or surrounding soft tissue, ligaments or tendons.
4) Referred Pain

Excessive biomechanical stress in amputees may cause painful musculoskeletal conditions such as sacroiliac dysfunction, piriformis syndrome, facet syndrome or radiculopathy.[31] Therefore it is important to examine posture and gait.

Furthermore, it is of value to examine skin for areas of ulceration and infection, palpate for areas of tenderness, bony exostosis, heterotropic ossification and adherent scar tissue and evaluate muscle strength and range of movement of neighbouring joints to exclude contracture formation.

THERAPY OF POST-AMPUTATION PAIN SYNDROMES

A survey by Sherman *et al*. in 1980 identified over 50 different therapies currently in use for the treatment of phantom limb pain.[32] This suggests clearly that an effective treatment of phantom limb pain has not been established and that 'the results are poor and usually below the expected rate of cure of pain with placebo treatment alone.'

Randomised controlled trials have only established the effectiveness of a small number of therapies.

However, as early treatment is more effective and often multidisciplinary approaches are needed, patients with severe postamputation pain should be promptly referred to a multidisciplinary pain clinic to ensure optimal and timely pain management.

Calcitonin

The parenteral administration of calcitonin is a proven treatment for phantom limb pain and in our experience the most effective in early stages,[33] while there is no benefit in chronic phantom limb pain.[34] After initial anecdotal reports,[35] a randomised double-blind cross-over study by Jaeger and Maier showed excellent effectiveness.[36] 200 IU of salmon calcitonin was given as an intravenous infusion over 20 minutes and provided complete pain relief for 76% of patients; 71% did not experience recurrence of their phantom pain. Calcitonin may also be given subcutaneously or intra-nasally.[33]

The mechanism of action of calcitonin in inhibition or modulation of pain perception is unknown; however anecdotal descriptions of its effectiveness in a number of states of central sensitisation are published. Side effects including dysaesthesia, nausea and vomiting have been described, but most are transient and can be prevented by prophylactic use of anti-emetics.[36] The risk of an anaphylactic reaction is most likely minimal, but needs to be considered.

Ketamine

Ketamine, an antagonist of the NMDA receptor, is another proven treatment of stump and phantom limb pain. In a randomised trial of patients with existing pain, ketamine has been shown to significantly reduce phantom pain and stump pain. It was also shown to decrease wind-up like pain (pain evoked by repetitive mechanical stimuli), and to increase the pain-pressure threshold in patients with phantom pain and stump pain. It was given as a bolus of 0.1mg/kg/5minutes followed by an infusion of 7mcg/kg/minute. Pain recurred 30minutes after discontinuation of the infusion in most patients.[15] This was confirmed in a more recent trial.[34]

Over-activity of NMDA receptors may be a factor in the maintenance of stump pain and phantom pain.

Analgesic and Co-analgesics Compounds

As outlined in the chapter 'Treatment of Neuropathic Pain', these agents can play an

important role in pain due to nerve injury, but have only variable effects in phantom limb pain.

Opioids

Generally, neuropathic pain is less responsive to opioids than nociceptive pain.[37] However, a randomised double-blind study of oral retarded morphine sulphate (MST) showed a significant reduction in phantom pain in opioid-sensitive patients, with pain reduction of over 50% occurring in 42% of patients. Neuromagnetic source imaging of three patients suggested reduced cortical reorganization may be occurring with the use of MST.[38]

A study comparing the effects of intravenous lidocaine with intravenous morphine showed that morphine given as 0.05mg/kg bolus followed by 0.2mg/kg infusion over 40 minutes, given on three consecutive days, significantly reduced both stump and phantom pain.[39] An NNT of 5.6 and superiority over mexilitine was found for morphine in a more recent trial.[40] Tramadol was as effective as amitriptyline in treating post-amputation pain.[41]

Gabapentin

In a randomized, double-blind, placebo-controlled, cross-over study, six weeks of gabapentin was better than placebo in relieving phantom limb pain. Pain intensity difference was significantly greater for gabapentin than for placebo.[42] These findings were not confirmed by a later study.[43]

Clonazepam

Anecdotal evidence suggests that clonazepam may be useful in the treatment of phantom pain.[44] There are however no studies to confirm this.

Lidocaine

A randomised double blind study comparing the effects of intravenous lidocaine with intravenous morphine showed that lidocaine given as 1mg/kg bolus followed by 4mg/kg infusion, given on three consecutive days, significantly reduced stump pain but had no effect on phantom pain.[39]

Carbamazepine

There is only anecdotal evidence for the use of carbamazepine in the treatment of post-amputation syndromes.[45] It has been extensively used in the treatment of other neuropathic pain states. Side effects can be problematic. Randomised trials are required.

Tricyclic Antidepressants (TCA)

In a randomised trial, chlorimipramine, a serotonin reuptake inhibitor, was found to be significantly better than nortriptyline, a noradrenaline reuptake inhibitor, in the treatment of central pain syndromes.[46] Amitriptyline and tramadol were equally effective in the treatment of phantom limb pain.[41]

Selective Serotonin Reuptake Inhibitors

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor with a side-effect profile significantly better than TCAs.[47] There are no RCTs on its effect on post-amputation pain syndromes.

Baclofen

This gamma-aminobutyric acid (GABA) agonist, when given intrathecally, has been shown to reduce chronic musculoskeletal pain.[48] It may therefore be of some benefit if muscle spasm is the source of the pain. It has not been proven to be of use in phantom limb pain.

Capsaicin

Capsaicin depletes the neurotransmitter, substance P from sensory nerves and may give relief to some patients with stump pain when used topically.[49]

Symptomatic Treatment of Pain Components

The burning component of phantom limb pain alone can be decreased by pharmacological and behavioural therapies that increase the temperature of the stump such as sympathectomy, α- or β-blockade or biofeedback.

Cramping can be relieved by treatments that reduce muscle tension, for example with the use of baclofen or again biofeedback.

Nonpharmacological Therapies

The following therapies are thought to relieve phantom pain by causing increased sensory inflow into the stump area:

- TENS
- Acupuncture
- Physical therapy

With the development of theories on cortical reorganisation as a cause for phantom limb pain, there are now therapies tried, which are based on the concept of reversing such reorganisation.[18] Sensory discrimination training programs show promise here; this is a process during which patients have to discriminate the frequency or location of high intensity, non-painful electrical stimuli applied through electrodes on their stump in an attempt to separate merged regions on their cortical somatosensory map.

A recent study using this technique showed that phantom limb pain was significantly decreased in the group who underwent the training process compared to controls. Cortical reorganisation, assessed by neuroelectric source imaging and structural magnetic resonance imaging, was also reduced in this group.[50] Mental imagery of limb movement[51,52] and a combination of laterality recognition, mirror movements and imagined movements are other successful approaches based on this concept.[53]

Similarly, there are now first data, that use of a myoelectric prosthesis may prevent cortical reorganisation and phantom limb pain.[54]

Invasive Therapies

Electroconvulsive Therapy (ECT)

This psychiatric treatment is thought to interrupt the dynamic reverberations that maintain central and phantom pain in the thalamocortical pathway[19] and has been used in the treatment of refractory phantom pain.[55] There have been no trials in this area.

Nerve Blockade

There is only anecdotal evidence for the use of peripheral nerve blockade in the treatment of phantom pain syndromes.[56] There have been no trials in this area.

Spinal Cord Stimulation

This treatment, thought to facilitate inhibitory descending pathways, has been described in the treatment of phantom pain. The overall success rate of this expensive and invasive approach in this indication is in the range of less than 50%.[57,58]

Implantable Intrathecal Delivery Systems

Infusing clonidine, local anesthetic, baclofen or opioids, usually in a combination, may be beneficial in selected patients with phantom limb pain, although there are no definitive studies.

Dorsal Root Entry Zone (DREZ) Lesions

DREZ lesioning has a limited effect for a limited time only in phantom limb pain;[59] this is in line with clinical experience with this neurodestructive approach. Other types of surgery and neuroablation often makes pain worse because of repeated stimulation and/or deafferentation of the affected nerves.

Psychological Therapy

Pre-amputation counselling is mandatory as amputees go through normal grieving processes. It is important to identify anxiety and depression early, as these can magnify pain perception. Behavioural, cognitive, group therapy and pain management programs are all useful methods of helping patients cope with their pain. Hypnosis, biofeedback and muscular relaxation training to disrupt the pain-anxiety-tension cycle are important components of chronic pain therapy. [60]

FUTURE AIMS

Future aims in the management of post amputation syndromes focus on:

1) Further prospective randomised trials to evaluate the benefits of current pharmacological therapies.
2) Clarification of the role of pre-emptive analgesia in the prevention of phantom pain.
3) Evaluation of the promising methods that attempt to revert the cortical reorganization that occurs following amputation towards normal.
4) A multi-modal and multi-disciplinary approach to pain management.

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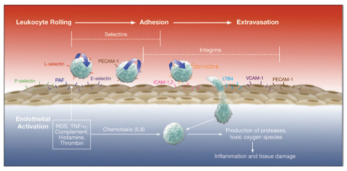

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