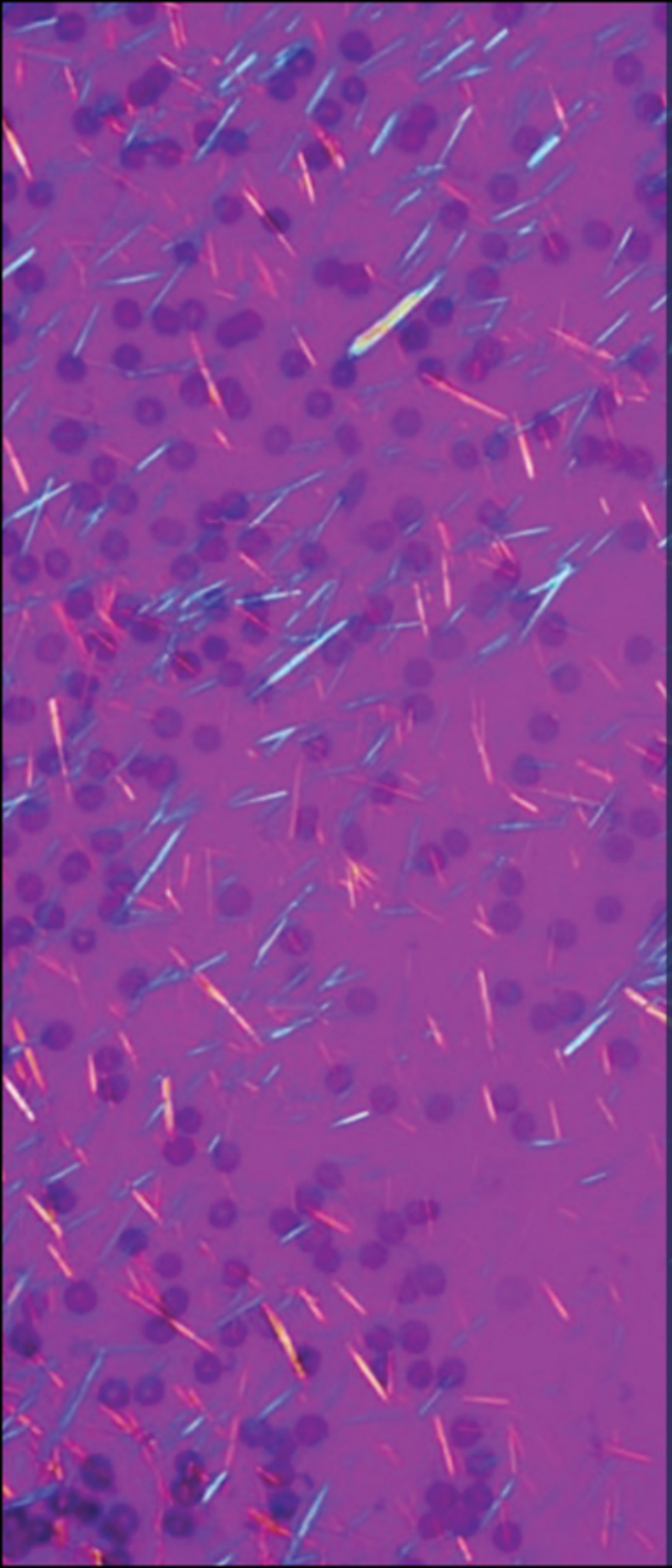

Pathology at a Glance

Second Edition

Barry Newell
Asma Z. Faruqi
Caroline Finlayson

WILEY Blackwell

Pathology at a Glance

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Second Edition

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We dedicate this book to our loving and supportive families.

Contents

Preface

We have greatly appreciated the feedback and comments received regarding the first edition of *Pathology at a Glance*. It is heartening to know that this guide to pathology, which aims to highlight the fundamental aspects of particular topics in the manner of a low-scale roadmap, has been useful to healthcare professionals at all stages of their careers.

Pathology is fundamental to medicine, and a good core knowledge helps immensely to unite the apparently disparate collections of signs, symptoms and facts encountered in the study of other medical and surgical disciplines.

Students, faced with limitless layers of information in detailed textbooks and online learning platforms, found this book gave a balanced overview and a framework onto which information gleaned from other sources could be added. Doctors from house officer to consultant have thanked us for simplifying their starting point for the preparation of presentations. *Pathology at a Glance* is also a popular revision aid.

Acknowledgements

We are indebted to those whose expertise contributed to the first edition and several people who kindly pointed out errors or areas in which new information has supervened, in particular Dr Joe Houghton.

Dr Kate Wheeler, Consultant in Paediatric Oncology, gave us invaluable help with the chapter on paediatric tumours in the second edition. Mr Colin Jardine-Brown's motivational skills and expert advice are also much appreciated (C.J.F.).

The help given in the first edition by Dr Jennifer Else (renal overview), Professor Neil Shepherd (*Helicobacter pylori*), Dr David Bevan (haemostasis), Professor Philip Butcher (tuberculosis), Professor Peter McCrorie (hypertension) and Dr Jonathan Williams (breast disease) continues to be greatly appreciated in the second edition of *Pathology at a Glance*.

Our thanks go also to the editorial staff for their patience and encouragement.

Barry Newell
Asma Z. Faruqi
Caroline Finlayson

Abbreviations

AC	alternating current
ACE	angiotensin-converting enzyme
ACS	acute coronary syndromes
ACTH	adrenocorticotrophic hormone
ADH	antidiuretic hormone
ADPKD	autosomal dominant polycystic kidney disease
AFP	alpha-fetoprotein
AIDS	acquired immune deficiency syndrome
AIH	autoimmune hepatitis
AIN	anal intraepithelial neoplasia; acute interstitial nephritis
ALD	alcoholic liver disease
ALL	acute lymphoblastic leukaemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMI	acute myocardial infarction
AML	acute myeloblastic leukaemia
ANCA	antineutrophil cytoplasmic antibody
APC	adenomatous polyposis coli
APTT	activated partial thromboplastin time
ARDS	adult respiratory distress syndrome
ASH	alcoholic steatohepatitis
AST	aspartate aminotransferase
ATN	acute tubular necrosis
ATP	adenosine triphosphate
AV	atrioventricular
BAL	bronchoalveolar lavage
BCC	basal cell carcinoma
BCG	bacille Calmette–Guérin
BCR	B cell receptor
BE	Barrett's oesophagus
BMI	body mass index
CA	coronary artery
cAMP	cyclic adenosine monophosphate
CARS	compensatory anti-inflammatory response syndrome
CBD	common bile duct
CCA	cholangiocarcinoma
CCK	cholecystokinin
CD	cluster of differentiation; coeliac disease
CF	cystic fibrosis
CFA	cryptogenic fibrosing alveolitis
CFTR	cystic fibrosis transmembrane conductance regulator
CFU	colony forming unit
CGIN	cervical glandular intraepithelial neoplasia
CHD	coronary heart disease
CIN	cervical intraepithelial neoplasia
CJD	Creutzfeldt–Jakob disease
CLL	chronic lymphocytic leukaemia
CML	chronic myeloid leukaemia
CMV	cytomegalovirus
CNS	central nervous system
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CRC	colorectal carcinoma
CrD	Crohn's disease
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
CVA	cerebrovascular accident
DAD	diffuse alveolar damage
DAI	diffuse axonal injury
DAMP	damage-associated molecular pattern
DC	direct current
DCC	deleted in colon cancer
DCIS	ductal carcinoma in situ
DIC	disseminated intravascular coagulation
DIP	desquamative interstitial pneumonia
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DPAS	diastase PAS
DU	duodenal peptic ulcer
dVIN	differentiated vulval intraepithelial neoplasia
DVT	deep venous thrombosis
EATCL	enteropathy-associated T-cell lymphoma
EBUS	endobronchial ultrasound
EBV	Epstein–Barr virus
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ENaC	epithelial sodium channel
ENT	ear, nose and throat
ER	endoplasmic reticulum
ERCP	endoscopic retrograde cholangiopancreatography
ESR	erythrocyte sedimentation rate
ESS	endometrial stromal sarcoma
ET	endothelin
FAP	familial adenomatous polyposis
FDC	follicle dendritic cell
FEV_1	forced expiratory volume in 1 second
FFA	free fatty acid
FFPE	formalin-fixed, paraffin-embedded
FGF	fibroblast growth factor
FNA	fine needle aspiration
FOB	faecal occult blood (test)
FSH	follicle-stimulating hormone
FVC	forced vital capacity
G6PD	glucose-6-phosphate dehydrogenase
GABA	gamma-aminobutyric acid
GALT	gut-associated lymphoid tissue
GBM	glomerular basement membrane
GC	gastric cancer
GDP	guanosine diphosphate
GFD	gluten-free diet
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
GH	growth hormone
GI	gastrointestinal
GN	glomerulonephritis
GORD	gastro-oesophageal reflux disease
GP	general practitioner
GTN	glyceryl trinitrate

GTP	guanosine triphosphate
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
Hb	haemoglobin
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HBOC	hereditary breast and ovarian cancer (syndrome)
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HDL	high density lipoprotein
HDV	hepatitis D virus
H&E	haematoxylin and eosin
HEV	hepatitis E virus; high endothelial venules
HGOC	high-grade ovarian serous carcinoma
HIAA	hydroxyindoleacetic acid
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HNPCC	hereditary non-polyposis colorectal carcinoma
H_2O_2	hydrogen peroxide
HP	*Helicobacter pylori*; hydrostatic pressure
HPV	human papillomavirus
HRSC	Hodgkin–Reed–Sternberg cell
HSIL	high-grade squamous intraepithelial lesion
hsp	heat shock protein
5HT	serotonin/5-hydroxytryptamine
IBD	inflammatory bowel disease
ICAM	intercellular adhesion molecule
IDC	invasive ductal carcinoma
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
INR	international normalised ratio
ISLN	in-situ lobular neoplasia
IUD	intrauterine device
IVC	inferior vena cava
JGA	juxtaglomerular apparatus
LAK	lymphokine-activated killer
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LH	luteinising hormone
LSIL	low-grade squamous intraepithelial lesion
MALT	mucosa-associated lymphoid tissue
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
MEN	multiple endocrine neoplasia
MGUS	monoclonal gammopathy of uncertain significance
MHC	major histocompatibility complex; mean haemoglobin concentration
MI	myocardial infarction
MMR	mismatch repair (enzymes)
MPD	myeloproliferative disease
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRCP	magnetic resonance cholangiopancreatography
mRNA	messenger RNA
MSI	microsatellite instability
NADP	nicotinamide-adenine-dinucleotide phosphate
NADPH	reduced NADP
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NET	neutrophil extracellular trap
NHL	non-Hodgkin lymphoma
NK	natural killer (cell)
NLPHL	nodular lymphocyte predominant Hodgkin lymphoma
NMDA	*N*-methyl-D-aspartate
NO	nitric oxide
NOS	not otherwise specified
NSAID	non-steroidal anti-inflammatory drug
NSGCT	non-seminomatous germ cell tumour
NSTEMI	non-ST-elevated myocardial infarction
PAF	platelet activating factor
PAH	polycyclic aromatic hydrocarbon
PAMP	pathogen-associated molecular pattern
PAN	polyarteritis nodosa
PAS	periodic acid–Schiff
PBC	primary biliary cholangitis
PE	pulmonary embolism
PEG-IFN	pegylated interferon
PGE	prostaglandin E
PHT	portal hypertension
PKD	polycystic kidney disease
PMN	polymorphonuclear neutrophil
PNET	primitive neuroectodermal tumour
POP	plasma oncotic pressure
PRR	pattern recognition sensor
PSA	prostate-specific antigen
PSC	primary sclerosing cholangitis
PTH	parathyroid hormone
PVC	polyvinyl chloride
RA	rheumatoid arthritis
RF	rheumatoid factor
RNA	ribonucleic acid
ROS	reactive oxygen species
SA	sinoatrial
SAME	syndrome of apparent mineralocorticoid excess
SBP	spontaneous bacterial peritonitis
SCC	squamous cell carcinoma
SCFA	short-chain fatty acids
SCID	severe combined immunodeficiency
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIRS	systemic inflammatory response syndrome
SLE	systemic lupus erythematosus
SMA	superior mesenteric artery
SMC	smooth muscle cell
SRBCT	small round blue cell tumour
SSL	sessile serrated lesion
STEMI	ST-elevated myocardial infarction
T4	thyroxine
TB	tuberculosis
Tc	T cytotoxic (cell)
TCR	T cell receptor
T2DM	type 2 diabetes mellitus
TF	tissue factor

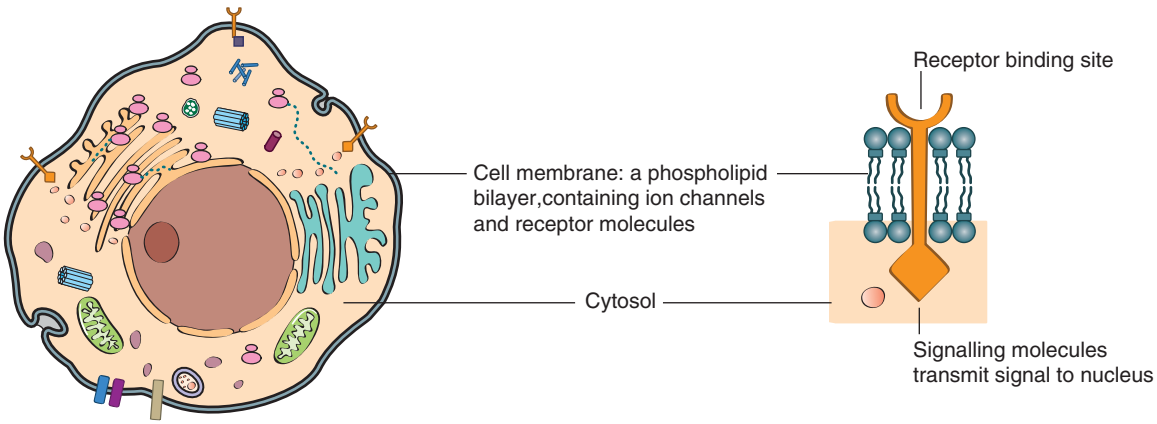
TDLU	terminal duct lobular unit
TGF	transforming growth factor
Th	T helper (cell)
TLR	Toll-like receptor
TNF	tumour necrosis factor
TSA	traditional serrated adenoma
TSG	tumour suppressor gene
TSH	thyroid-stimulating hormone
TT	thrombin time
UC	ulcerative colitis
UDCA	ursodeoxycholic acid
UIP	usual interstitial pneumonia
UTI	urinary tract infection
uVIN	usual vulval intraepithelial neoplasia
VEGF	vascular endothelial growth factor
VLDL	very low density lipoprotein
VOC	volatile organic compound
VSD	ventricular septal defect
vWF	von Willebrand factor
WCC	white cell count
WHO	World Health Organisation
WHR	waist/hip ratio
5YSR	five-year survival rate

General pathology

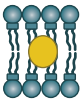
Introduction

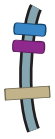
1 The normal human cell

Overview of the structure of normal human cells



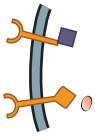
Controlling the intracellular environment: cell membrane and ion pumps


Phospholipid bilayer: hydrophilic ends on outer and inner aspects. Hydrophobic ends inside membrane, stabilised by cholesterol


Na/Cl pump

Calcium channel

Receiving signals


Cell surface receptors and second messengers

Intracellular transport, cell movement and mitosis


Centriole: spindle formation (cell division)

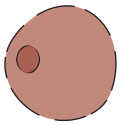

Cytoskeletal components: microtubules and filaments

Degradation/destruction


Lysosome


Peroxisome

Protein production and secretion


Nucleus


Ribosome and newly producedpeptide

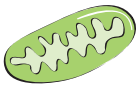

Rough (with ribosomes) and smooth endoplasmic reticulum


Golgi apparatus: protein modification (folding and addition of carbohydrate)


Secretory vesicle containing protein/glycoprotein product


Proteosome: degrades defective protein

Energy production


Mitochondrion

The important functions of the cell are: manufacture of proteins for local or distant use, energy generation, functions appropriate to tissue type and replication.

The main elements are the nucleus, the cytoplasm (cytosol), the cytoskeleton and the subcellular organelles, all bound by membranes.

Nucleus

The nuclear membrane contains pores to permit metabolites, RNA and ribosomal subunits in or out. It contains:

- DNA, the nuclear chromatin, which only forms about 20% of the nuclear mass.
- Nucleoli – ribosomal RNA synthesis and ribosome subunit assembly.
- Nucleoprotein, e.g. synthetic enzymes for DNA, RNA and regulatory proteins, all made in the cytoplasm and imported into the nucleus.
- Messenger, transfer and ribosomal RNA en route for the cytoplasm.

Cytosol

The nutritious fluid medium that bathes and supports the organelles, through which the cytoskeleton ramifies. Many reactions take place here.

Cytoskeleton

- Microtubules: organelles such as secretory vesicles or internalised receptors can be transported through the cell via the cytoskeleton.
- Microfilaments (actin, myosin): these stabilise cell shape and act as contractile proteins in muscle.
- Intermediate filaments, e.g. cytokeratin, desmin, neurofilament proteins and glial fibrillary acidic protein (the types differ between tissues and all are structural).

Organelles

Mitochondria

These are the main ATP/energy-generating organelles and house the Krebs cycle and oxidative phosphorylation. They have their own ssDNA (maternally derived) which codes a minority of their proteins. A porous outer membrane and folded inner membrane are present.

Ribosomes

Nucleolus-produced ribosomal subunits aggregate in the cytosol and attach to the endoplasmic reticulum or lie loose in the cytosol, depending on the destination of the protein to be made (free ribosomes make proteins for inside the cell itself). Ribosomes translate RNA strands into a correctly assembled amino acid sequence (peptide molecule).

Endoplasmic reticulum (ER)

The ER is an irregular maze of membrane-bound tubules, saccules and cisterns which ramifies through the cell.

- **Rough ER** is studded with ribosomes. Proteins made by the rough ER pass into the rough ER cisternae and undergo secondary folding and early glycosylation before being incorporated into membranes for export from the cell, receptor molecules on the cell, or components such as lysosomes within the cell.
- **Smooth ER**: there is a further addition of carbohydrate moieties to protein, folding to achieve tertiary structure.

Golgi apparatus – see diagram.

Secretory vesicles

These membrane-bound packets are moved via the cytoskeleton to fuse with the cell membrane to expel their contents outside.

Lysosomes

These are intracellular membrane-bound vesicles, containing destructive chemicals and enzymes, which fuse with phagosomes to release their contents into the phagolysosome and destroy pathogens. Lysosomes also degrade worn-out cell organelles (autophagy).

Peroxisomes

These small membrane-bound granules contain oxidative enzymes which make hydrogen peroxide plus its regulator catalase.

Proteasomes

These identify defective proteins and degrade them into their component peptides and amino acids for reuse by the cell. Portions of broken-down protein are bound by MHC class I molecules and displayed on the cell surface to Tc cells.

Centrosome

This contains the two linked centrioles, from which microtubules radiate into the cell. The centrioles duplicate and migrate to opposite ends of the cell during cell division, separating the duplicated chromosomes.

Membranes

Membranes are phospholipid barriers surrounding the cell itself and certain organelles. They isolate portions of the cell and permit several, often incompatible, metabolic processes to take place simultaneously.

The cell membrane

This phospholipid bilayer interacts with the extracellular world by assorted surface molecules. The centre is lipophilic and the surfaces hydrophilic, with cholesterol as a stabilising 'spacer' between them. The 'raft theory' suggests that intramembrane structures can float and be cross-linked around the perimeter of the cell.

Membrane proteins: proteins that project through the membrane outside the cell usually have attached carbohydrates. Glycolipids are carbohydrates attached to the lipid membrane and are important in cell recognition, cell–cell bonds and adsorbing molecules. Some tissues have a protective glycocalyx.

Transport through the cell membrane: the main mechanisms are as follows.

- Passive diffusion (needs only a concentration gradient), e.g. lipids and lipid-soluble agents like ethanol.
- Facilitated diffusion: the binding of a molecule triggers a conformational change which moves the molecule across the membrane.
- Active transport: against a concentration gradient to maintain ion concentrations within the cell, e.g. the Na^+/K^+-ATPase complex.
- Bulk transport: **endocytosis**, **transcytosis** and **exocytosis**. Endocytosis includes *receptor-mediated endocytosis* (ligands or viral

particles) and *phagocytosis* (engulfing of particles). *Pinocytosis*, the sampling of small quantities of extracellular fluid, is not receptor mediated.

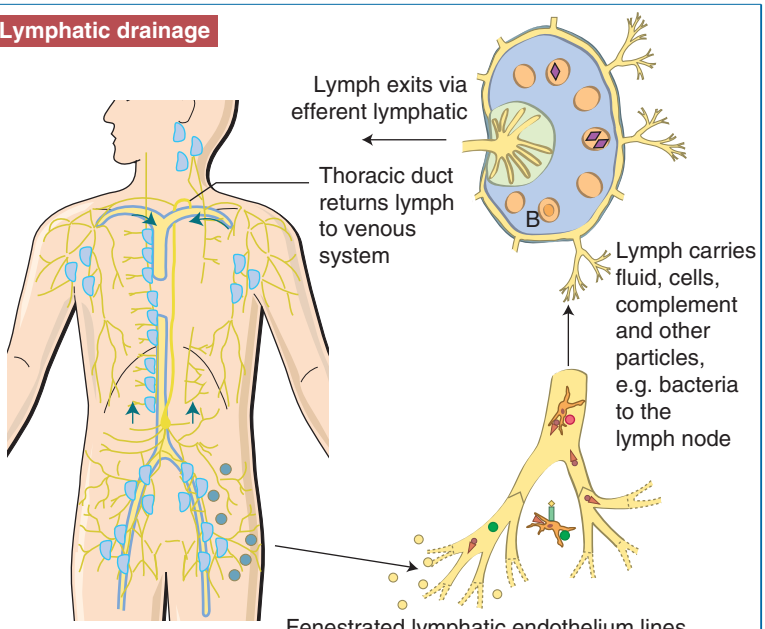
Transmission of messages across the cell membrane

- Lipid-soluble agents (e.g. steroids) diffuse directly across cell membranes.
- Receptor binding and activation of secondary messengers: applies to protein messenger molecules, which bind to a specific cell surface receptor (*ligand*), resulting in active transport of the molecule through the membrane or the triggering of intracellular cascade reactions.

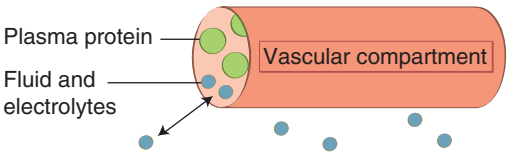
Neurotransmitters: these are chemical messengers for neurones or myocytes that cause an electrical response in the target by receptor-mediated opening of an ion channel.

2 Fluid dynamics

Lymphatic drainage

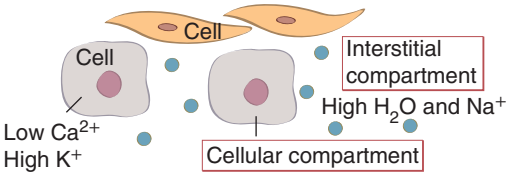


Compartmentalisation within the body



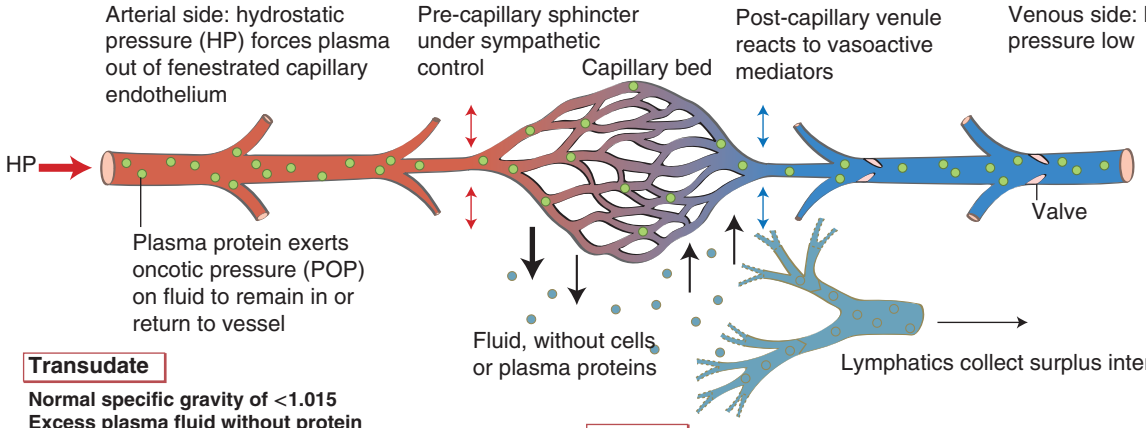
Fluid moves freely between the vascular and interstitial compartments, via the permeable capillary bed

Protein is retained within the vascular compartment by its large size and negative charge



Cell membranes tightly regulate their electrolyte contents using Na/K exchange and calcium pumps

Normal fluid movement



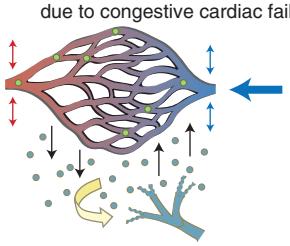
Transudate

Normal specific gravity of <1.015
Excess plasma fluid without protein
Fluid accumulates in tissues, exceeding capacity of lymphatics to drain it, causing 'pitting' oedema caused when:

The **plasma oncotic pressure drops,** e.g. decreased protein production by the liver in chronic liver disease, or protein loss via the kidneys in nephrotic syndrome

Plasma protein retained in vessels, fluid is pressed out of vessels into the interstitium
Oedema occurs if lymphatic drainage cannot meet demand

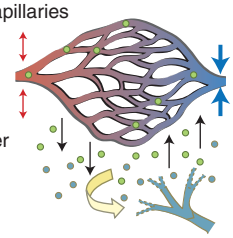
The **hydrostatic pressure increases,** e.g. back-pressure due to congestive cardiac failure



Exudate

Specific gravity > 1.015
Excess plasma fluid with protein
Example: inflammation, vascular response to inflammatory mediators:

- Constriction of post-capillary venules increases hydrostatic pressure
- Endothelial cells contract, enlarging the space between cells
- Both fluid *and* plasma proteins move out of capillaries into the interstitium
- Loss of plasma proteins reduces the osmotic pull on fluid to return to the blood vessels
- Increased quantities of fluid, plus any cells, complement proteins or micro-organisms enter the lymph, but drainage cannot meet demand and fluid remains in the interstitium



Approximately 70% of the body is composed of water. Water provides the essence of the fluid medium for the transport of cells, nutrients and waste products between organs, provides substance for cellular cytosol and is the solvent in which numerous chemical reactions occur. Disruptions of the quantity of water in the body and its distribution can have serious consequences.

Discussions of fluid balance tend to revolve around a compartmental model of fluid distribution. Three main compartments are described: the intracellular (66%), interstitial/intercellular (25%) and intravascular (7%). A fourth compartment of specialised fluids (2%) can also be considered and includes secretions of the gastrointestinal (GI) tract, peritoneal and pleural fluids, cerebrospinal fluid, synovial fluid, intraocular fluid and the vestibulocochlear fluids. The fourth compartment is often amalgamated into the interstitial.

Fluid movement is dynamic between all of the compartments and tends to follow passive osmotic and hydrostatic gradients, provided that the membrane separating the compartments is water permeable. If water movement between body compartments is required, manipulation of these gradients is typically the method by which this is accomplished. For example, the secretion of sweat involves the pumping of sodium and chloride ions into the lumen of the sweat duct. Water then follows passively through membrane pores and intercellular junctions.

Electrolytes

Electrolytes are one of the main classes of solute within body water. The chief intracellular cation is potassium and the principal extracellular cation is sodium. This differential distribution of sodium and potassium is maintained by the Na^+/K^+-ATPase that is present on effectively all cells. It is the basis for the electrical activity of neurones, skeletal muscle and cardiac muscle. Alterations in the extracellular concentration of either potassium or sodium can destabilise the electrically excitable membranes of these cells, generating aberrant electrical activity such as seizures, arrhythmias or muscle weakness.

Electrolyte concentrations are also vital in maintaining turgor within cells. If the osmolarity of extracellular fluid is disturbed, water will move in or out of cells accordingly, resulting in cell swelling (and ultimately rupture) or shrinkage. Such are the potentially catastrophic effects of this inappropriate movement of water that body osmolarity is extremely tightly regulated by the antidiuretic hormone (ADH) system. In extreme situations, homeostatic mechanisms will strive to preserve blood osmolarity (which is in equilibrium with that of the other compartments) even at the expense of electrolyte levels and other parameters.

Blood and blood filtration

The vascular compartment contains 70 mL of blood per kilogram body weight (hence 4900 mL for a 70-kg man). Cellular constituents (erythrocytes, leucocytes and platelets) comprise 40% of this volume, while the remaining 60% is plasma. Plasma is water in which electrolytes, numerous types of proteins and lipoproteins are dissolved. Blood serves as a transport medium to deliver nutrients to the tissues and to remove waste products from them. This movement of nutrients and metabolites occurs at the capillary level.

When blood reaches the capillaries, fluid and electrolytes can pass easily through the gaps between endothelial cells, but cells and larger molecules (proteins) cannot. This movement is bidirectional and the direction that dominates is regulated by the balance between the hydrostatic pressure (HP) exerted by the blood pressure generated by the heart and transmitted through the vascular tree and the plasma oncotic pressure (POP) generated by plasma proteins. The HP drives water from the blood into the tissues whereas the POP provides a gradient that draws fluid back into the blood from the extracellular space.

In the proximal capillary bed, HP exceeds POP and there is a net movement of fluid from the blood into the extracellular space. The interstitial fluid is in equilibrium with the intercellular fluid and there is ready movement of nutrients and metabolites between these two compartments. However, the HP falls across the capillary bed and on the distal side is overpowered by the oncotic pressure, causing a net movement of fluid and its accompanying solutes back into the blood. Nevertheless, the action of the POP is not complete and a small quantity of fluid remains in the extracellular space. This is lymph and is handled by the lymphatic drainage system.

Lymphatic system

Lymphatic vessels commence in the tissues as blind-ended tubes lined by fenestrated endothelium. The lymph is massaged through progressively larger and more valve-bearing, muscularised (non-leaky) vessels to the thoracic duct, which empties into the venous system via the superior vena cava, returning the fluid to the circulation. En route, lymph is sieved through lymph nodes and thus lymph has a vital role in presenting extracellular material to the immune system.

Transudates

A transudate is an abnormal accumulation of fluid that has a low concentration of protein (typically defined as less than blood albumin). Transudates may occur in numerous locations, including the pleural and peritoneal cavities, and arise for one of two reasons.

1 *Increased hydrostatic pressure*, typically back pressure within the venous system due to inadequate cardiac function. Fluid accumulates in the extracellular compartment and yields 'pitting' oedema of the skin. Pleural effusions may also be seen.

2 The *plasma oncotic pressure drops* due to either decreased hepatic protein synthesis (as in cirrhosis) or excessive protein loss via the kidneys (nephrotic syndrome). As well as pitting oedema, ascites and pleural effusions are common.

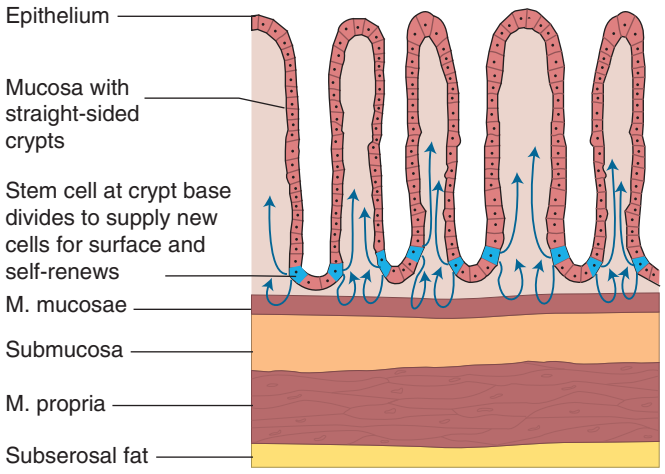
Exudate

An exudate is an abnormal collection of fluid that has a high protein concentration, typically greater than plasma albumin. Exudates are caused by inflammatory processes that markedly increase the leakiness of the capillary bed such that proteins that would not normally be able to leave the circulation are now able to. Constriction of post-capillary venules raises the hydrostatic pressure and also contributes to exudate formation.

Tissue damage

3 Tissue types and the effect of tissue damage

Tissue replacement by stem cells, e.g. colon



Cell types

Epithelium:
Covers surfaces, cells bind each other to form an impermeable barrier. Specialised to local needs

Neuroectoderm: Neurons, melanocytes and neuroendocrine cells

Haemopoeiticand lymphoreticular
Bone marrow-derived cells and their precursors.
Mature cells are mobile, many circulate

Connective ('soft') tissue:
Supporting tissues, e.g. fat, bone, fibrous tissue, nerve insulation, cartilage, muscle (smooth, striated, cardiac)
Endothelium lines vascular system

Germ cells:
Haploid generative cells in testis and ovary

Placenta
Trophoblast

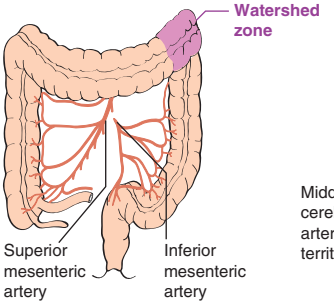
The effects of damage depends on the tissue type affected and the type of damaging agent

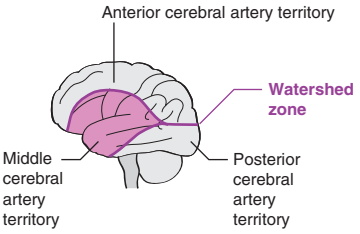
Labile cells
Constantly self-renewing, e.g. bone marrow derived cells, epithelium: generally have short lifespan, high turnover; are quick to regenerate following trauma. Liable to damage by radiation or chemotherapeutic drugs,which affect cells undergoing mitosis

Stable cells
Self-renew as required, from stem cells or mature cells. May divide in limited fashion. Long lifespan tissues, e.g. liver, regenerate effectively following injury if sufficient normal liver remains. Fibroblast and endothelial cell proliferation is essential for healing and repair in many tissues

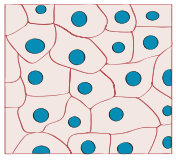
Permanent cells
Long lifespan, little or no capacity to self-renew, e.g. brain, cardiac muscle. Damage causes tissue loss: in the heart, scar tissue forms; in the brain the tissue liquefies

Most damaging agents affect tissues directly, but watershed zone infarction can occur as an indirect consequence of diminished blood flow at the 'watershed' between zones supplied by end-arteries

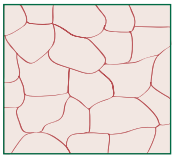




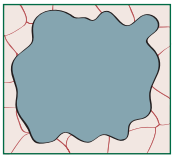
The two main types of cell death, coagulative and liquefactive necrosis, and distinctive histological subtypes: fibrinoid, caseous and fat necrosis. The clinical observation of "gangrenous necrosis" refers to blackened, ischaemic extremities: dry gangrene is due to infarction (coagulative necrosis) and wet gangrene has superadded infection, causing liquefaction



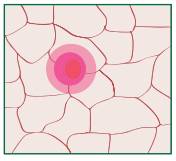
Normal tissue:
Cells have nuclei and distinct cell outlines



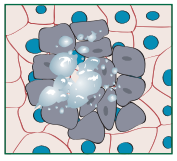
Coagulative necrosis
Example, renal infarct: cell outline preserved but cell contents degenerate



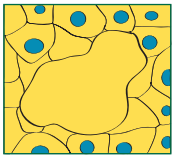
Liquefactive necrosis
Necrotic material liquefies, e.g. brain, abscess contents



Fibrinoid necrosis
Blood vessel destruction by eosinophilic 'fibrinoid' material, e.g. vasculitis.



Caseous necrosis
Tuberculosis – crumbly necrotic debris, combining coagulative and liquefactive features: granulomatous reaction



Fat necrosis
Follows trauma and forms hard nodule which can be mistaken for tumour (e.g. in breast)

Normal tissue types

Epithelium

Epithelium, derived from embryonal ectoderm*, lines the body's surfaces. It constantly regenerates and heals quickly. The three main epithelial subtypes are:

1 **Squamous**: functions as a barrier and protects against friction.
   a. *Stratified squamous*: covers skin, pharynx, tongue, oesophagus, anus, vagina, external auditory canal; keratinisation is only normally seen in the skin.
   b. *Simple squamous*: forms mesothelium lining the pleural and peritoneal cavities. Pathologists regard endothelium as a separate entity from simple squamous epithelium (See Note below).
2 **Glandular**: lines all secretory organs. Its functions include:
   a. *Secretion*:
      • Non-specialised, e.g. mucin, to trap bacteria in the nose or assist food transit in gut.
      • Specialised, e.g. hormone or acid secretion (gastric parietal) or absorption (gut, renal tubules).
   b. *Ion transfer*: renal tubules.
   c. *Clearance*: ciliated bronchial cells remove inhaled particles stuck in mucin (mucociliary escalator).
3 **Urothelial (formerly 'transitional')**: this 'pseudostratified' epithelium lines the urinary tract. It contains *umbrella* cells that maintain the integrity of the surface on stretching to accommodate urine.

Note: Mesothelial cells, the single-layed simple epithelium lining the pleural and peritoneal cavities, are derived from mesoderm, but contain keratins. Endothelium (see later) is often described by non-pathologists as a simple squamous epithelium, but endothelial cells do not contain keratin fibres, a defining feature of epithelium (they are supported by vimentin fibres). Note that synovial cavities are not lined by epithelial cells, but by two cell types, derived from fibroblasts and macrophages.

Neuroectodermal-derived tissue

This forms the central and peripheral nervous system. Scattered neuroendocrine cells populate various epithelia and secrete site-specific substances, e.g. skin melanocytes, gut hormone-secreting cells and in the bronchus (where they are thought to give rise to pulmonary small cell carcinoma).

Connective tissue

This forms structural tissues.

• **Fat** (adipo-) stores lipid, can regenerate and may secrete or respond to cytokines. Adipokines can drive inflammation.

• **Bone** (osteo-) consists mainly of matrix-containing sparse osteocytes and is constantly remodelled by osteoblasts, which lay down matrix, and osteoclasts, which resorb it, in response to physical stresses and hormones (e.g. parathyroid hormone or calcitonin). It heals excellently.

• **Fibrous tissue** (fibro-), such as tendon, which consists mainly of acellular and avascular collagenous tissue and heals poorly.

• **Cartilage** (chondro-) consists mainly of avascular matrix, in which a few chondrocytes are embedded; it heals poorly.

• **Nerve sheath** (neurofibro-) there are several nerve sheath components, which may undergo benign proliferation, e.g. after amputation, or form malignant tumours. Myelin is made by Schwann cells, which can form schwannomas.

• **Smooth muscle** (leio-) forms the walls of medium-sized and large blood vessels and lymphatics, the uterine myometrium, the vaginal wall and the muscular layers of the GI, respiratory and urological tracts. It can regenerate but often heals by scarring.

• **Striated muscle** ((rhabdo)myo-) forms voluntary muscle. Regeneration is limited.

• **Cardiac muscle**: myocardium only; does not regenerate.

• **Endothelium** arises from 'blood islands' of the embryonal mesoderm. Different types line the blood vessels, lymphatics and the hepatic and splenic sinusoids. Endothelium readily regenerates.

Haemopoietic and lymphoreticular tissue

These tissues generate blood cells and form the immune system. They are discussed in Chapters 8–12.

Germ cells

These are the ovarian and testicular reproductive cells. They are constantly produced by the testis; the ovary contains a finite number from birth.

Proliferative and regenerative capacity

• **Labile tissues** readily regenerate and constantly proliferate in life, e.g. the epithelia of the skin, gastrointestinal tract, bronchus.

• **Stable tissues** include the liver and kidney, and can, if necessary, regenerate but usually show only very limited cell turnover. The liver has huge regenerative capacity: over half can be removed yet the remainder can undergo compensatory regeneration. Renal tubules are quick to regenerate following damage such as transient ischaemia.

• **Permanent tissues** show little to no regeneration so cell death can be catastrophic (e.g. cardiac myocytes, neurones).

Stem cells are progenitor cells that can potentially form any tissue but respond to local hormones and cytokines to yield cells appropriate to the place in which they are generated. Stem cells divide to form a copy of themselves (and are thus immortal) plus a population of 'committed' progenitor cells. These divide into 'transit amplifying cells' and after several cell divisions yield terminally differentiated cells which die once their lifespan is over, to be replaced by further stem cell progeny.

Cell replacement in tissues with a high turnover is by stem cells. In tissues such as liver, with a low cell turnover, replacement of individually damaged cells is by division of adjacent cells, but larger amounts of hepatocyte loss requires stem cells for replacement. Each tissue has a compartment containing its own stem cell.

Tissue necrosis

Necrosis is a form of unregulated cell death which has a variety of causes, chiefly physical trauma, infarction, infection or chemicals. The appearance of necrosis varies according to the stimulus and the tissue. The major types are as follows.

• **Coagulative necrosis** due to ischaemia is commonest and usually appears as a firm, pale, wedge-shaped region of tissue reflecting the territory supplied by an occluded arteriole. The cells retain their shape but lose their nuclei and are known as 'ghost cells'.

• **Liquefactive necrosis** typically affects the central nervous system (CNS), often after a stroke. Once the damaged tissue has been cleared there is no healing and no scar, and only a cystic space remains; the mechanism is not well understood. Abscesses also

show liquefactive necrosis, due to enzymic digestion of tissues by the infecting organism.

• **Caseation** is a white, crumbly, cottage cheese-like appearance found in tuberculosis and some fungal infections. It is a mixture of coagulative and liquefactive necrosis.

• **Fat necrosis**: hard, bright yellow nodules of fat necrosis occur, possibly secondary to trauma and may become calcified and resemble tumour clinically. Digestion of fat by pancreatic enzymes with fat necrosis and calcification is commonly seen in acute and chronic pancreatitis.

Types of infarction

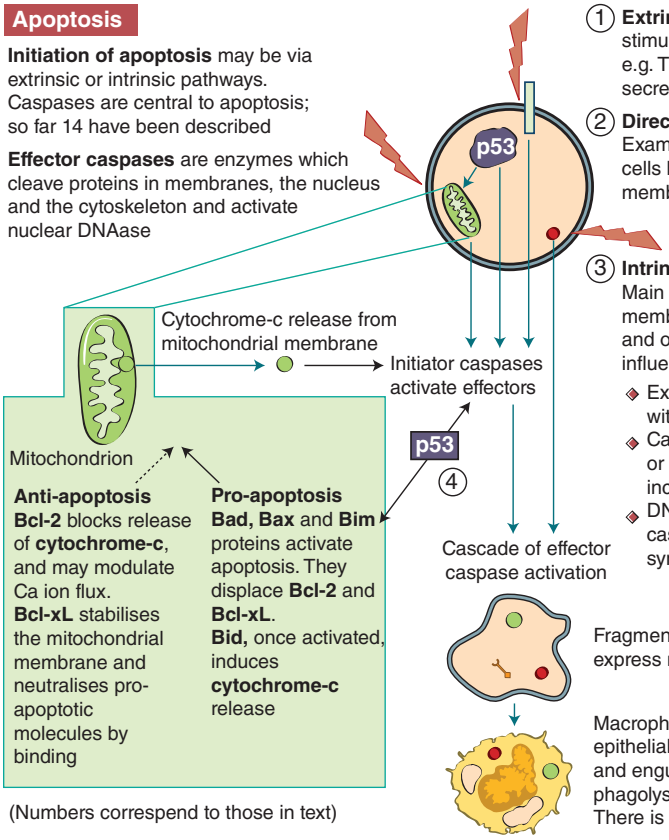
Infarction is necrosis of a tissue or organ due to disruption of its blood supply. In *arterial* infarction there is inadequate flow into the organ. In *venous* infarction the outflow is obstructed, preventing flow through the organ and causing congestion and stagnation. Arterial infarction is typically due to occlusion of the vessel by a thrombus or embolus; external compression is rare. Venous infarction often reflects compression of the veins, as occurs in strangulation of a hernia. *Watershed zone* infarctions are illustrated opposite.

4 Cell death

Apoptosis

Initiation of apoptosis may be via extrinsic or intrinsic pathways. Caspases are central to apoptosis; so far 14 have been described

Effector caspases are enzymes which cleave proteins in membranes, the nucleus and the cytoskeleton and activate nuclear DNAase



① **Extrinsic** 'death receptor' pathway stimulated by cross-linking receptors, e.g. TNFR1, Fas. Example: TNF secretion by immune cells

② **Direct activation**
Example: Granzyme B injected into cells by Tc cells through holes in membranes made by perforin

③ **Intrinsic activation**
Main pathway is by mitochondrial membrane release of cytochrome c and other pro-apoptotic molecules, influenced by Bcl-2 family members

- Example: growth factor blockage/ withdrawal
- Can be stimulated by autophagic or necrotic mechanisms which increase Ca^{++} levels in cytosol
- DNA damage via p53 stimulates caspases directly or through the synthesis of Bax and Bak

Anti-apoptosis
Bcl-2 blocks release of **cytochrome-c**, and may modulate Ca ion flux.
Bcl-xL stabilises the mitochondrial membrane and neutralises pro-apoptotic molecules by binding

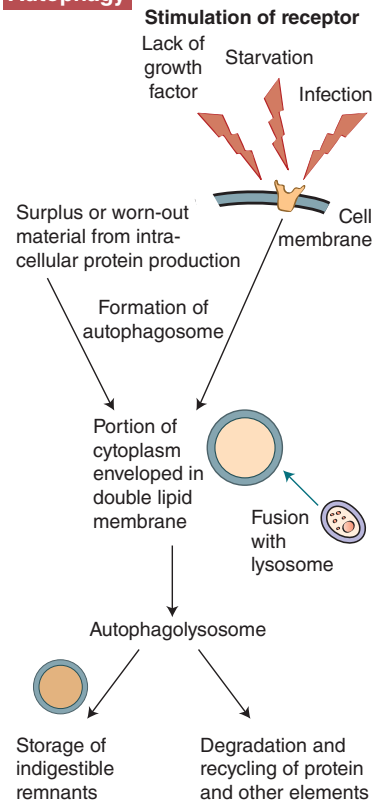
Pro-apoptosis
Bad, Bax and **Bim** proteins activate apoptosis. They displace **Bcl-2** and **Bcl-xL**.
Bid, once activated, induces **cytochrome-c** release

Fragments bud off the cell surface and express new ligands. The cell shrinks

Macrophages and some adjacent epithelial cells attach to the ligands and engulf the debris, digesting it in phagolysosomes.
There is no acute inflammation

(Numbers correspond to those in text)

Autophagy

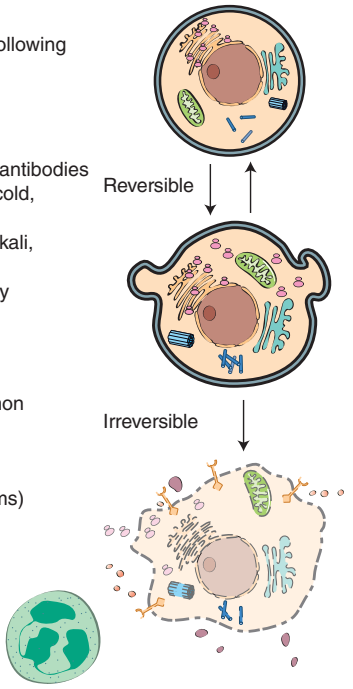


Necrosis

Agents which cause necrosis fall into the following main categories:

- **Ischaemia, hypoxia or re-perfusion,** e.g. myocardial infarction
- **Infection,** e.g. bacterial, viral, fungal
- **Immune-mediated,** e.g. cross-reacting antibodies
- **Physical agents,** e.g. extreme heat or cold, electrocution, irradiation
- **Chemical agents,** e.g. strong acid or alkali, drugs which bind DNA
- **Nutritional,** e.g. folic acid/B12 deficiency

The generation of **free radicals** is a common effector pathway (oxidative stress occurs when there is more generation of reactive oxygen species (free radicals) than can be cleared by the available scavenging systems)



- Na/K pump in the cell membrane fails, e.g. loss of ATP production by mitochondria. Lactic acid may accumulate
- Na^{+} enters the cell, passively accompanied by water. The cell swells
- Ca/Mg pump fails: excess cytosol Ca^{++} activates enzymes which deplete ATP
- The membranes bleb and ribosomes dissociate from endoplasmic reticulum, cytoskeletal components clump
- The situation is still reversible
- Enzymes activated by Ca^{++} digest the cell membrane, cytoskeleton and the nuclear chromatin
- The damage is irreversible
- Various nuclear changes may occur: it may shrink and get darker (pyknosis), fade away (karyolysis) or fragment (karyorrhexis). Similar nuclear changes are seen in apoptosis, particularly karyorrhexis. Some claim that this appearance is unique to apoptosis but it is disputed
- Release of cell contents stimulates acute inflammation. This adds to the damage by releasing further digestive enzymes and free radicals into the tissue
- If proteolytic digestion predominates there is less inflammation and the result is coagulative necrosis
  If hydrolytic enzyme digestion predominates, the tissue undergoes liquefaction

In the living person, cell death occurs all the time and is often a necessary process. The two mechanisms that produce cell death are apoptosis and necrosis. It is becoming clear that these entities are not always distinct, but generalisations are made below.

Apoptosis

Apoptosis, often called 'programmed cell death', occurs during embryological development, as new tissues are formed and remodelled, or in physiological cycles such as the menstrual cycle. Apoptosis is characterised by the orderly breakdown of cellular constituents, which are packaged into membrane-bound vesicles and tagged for collection by phagocytes. This requires energy.

The initiation of apoptosis is as follows.

1 Binding of a 'death ligand' (e.g. TNFR1 or Fas) on the cell surface, e.g. direct binding by T cells or NK cells, or tumour necrosis factor (TNF) secretion by immune cells.

2 Membrane disruption by perforin, then intracellular injection of granzyme B by a cytotoxic T cell (Chapter 10).

3 Release of pro-apoptotic proteins, e.g. cytochrome *c*, from leaky mitochondrial membranes, a process largely regulated by pro- and anti-apoptotic proteins of the Bcl-2 family.

4 *TP53*, a 'gatekeeper' gene in the cell cycle. p53 protein instigates apoptosis if there is a failure to repair DNA damage (Chapter 26).

Once started, apoptosis is generally irreversible, involving a final common pathway of an intracellular cascade of caspases. Proteolytic cleavage of cell contents and water loss causes cell shrinkage. Fragments bud off, enveloped by cell membrane, which expresses new ligands. Apoptosis does not stimulate an acute inflammatory response; instead, macrophages and adjacent cells bind the new ligands and phagocytose the fragments.

Necrosis

The death of a group of cells due to a noxious stimulus is referred to as necrosis. Necrosis is caused by many physical and chemical agents, amongst the most common of which are ischaemia, infection and drugs (e.g. chemotherapy). Necrotic cellular debris stimulates an acute inflammatory response which may increase the area of tissue damaged due to the leakage of lysosomal enzymes from polymorphs and macrophages.

It has been suggested that necrosis is what happens after cell death (i.e. irreversible damage) and that changes up to this point, which can be reversed, should be classed as cell damage. The point of no return is best recognised when there is a loss of membrane integrity and influx of calcium into the cytosol from the interstitial fluid or from the endoplasmic reticulum.

Factors that influence whether the damage is reversible include:

- **The duration of the stimulus**, e.g. ischaemia due to coronary artery thrombosis will cause myocardial infarction, but if the occlusion is rapidly cleared the area of cardiac muscle that dies will be reduced (Chapter 36). Reperfusion may cause problems due to the release of free radicals in the reperfused territory.
- **The dose of a chemical agent**: what can cause cell death in some people, does not in others due to genetic polymorphism (variation in inherited genes encoding the liver enzymes that metabolise the drugs).
- **The tissue type and its metabolic activity**: the neurones of the brain and cardiac muscle cells are highly metabolically active. Energy production from glycolysis via anaerobic pathways is available for liver or muscle (which store starch) but produces toxic lactic acid within the cell. Damage begins within minutes in the brain, but limb striated muscles can be deprived of oxygen for several hours. Cooling of tissues reduces their metabolism and increases survival time.
- **The state of health of the existing tissue**, e.g. iron overload in haemochromatosis renders the liver more susceptible to damage by other toxins, like alcohol.

Autophagy

The body attempts to preserve cells through times of adversity by undergoing autophagy, a particular type of cellular adaptation commonly seen in starvation and also in infection. It is also initiated by growth factor deprivation.

Portions of cytoplasm are bound by membranes to form a vesicle (autophagosome), which fuses with a lysosome and its contents, once degraded by hydrolase enzymes, are then recycled. The process is like hibernation and can be reversed once the lean times pass, but if taken to extremes because the stimulus persists, the cell dies either by apoptosis or necrosis.

Pathological examples of diseases in which autophagy plays an important role include neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases. Much interest has recently developed in the role played by autophagy in cancer.

Free radicals

Free radicals are highly reactive anions with an unpaired outer orbital electron. They react with inorganic or organic chemicals to form further free radicals. Important examples are:

- Reactive oxygen species (ROS): hydrogen peroxide (H_2O_2), superoxide anion radical ($O^{2-}\cdot$) and hydroxyl radical ($\cdot OH$).
- Nitric oxide (NO) made by endothelium, macrophages, neurones and other cells.

Formation

- During normal cellular energy generation by oxygen reduction and electron transfer.
- Killing of pathogens by phagocytes: ROS are preformed in a membrane complex.
- Unwanted by-product of intracellular oxidase reactions.
- Radiation (generates hydroxyl and hydrogen free radicals by ionising water).
- Toxic by-product of drug/chemical metabolism by cellular enzymes, e.g. in the liver.

Harmful effects

- Lipid membrane damage by peroxidation (affects the cell membrane and the membranes of organelles).
- Protein damage by amino acid oxidation, cross-linkages or protein breakdown, e.g. microtubule aggregation.
- DNA damage can cause mutations and cancer.

Protection

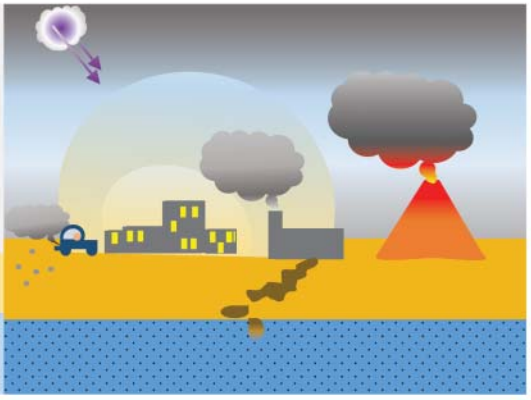
- Natural decay to oxygen and H_2O_2.
- Antioxidants, e.g. glutathione and vitamins A, C and E.
- Binding of copper and iron to transport proteins.
- Scavenging enzymes that break down H_2O_2 and superoxide anion, e.g. catalase, superoxide dismutases or glutathione peroxidase.

5 Harmful agents in the environment

Environmental pollution

***Air pollution alone is estimated to cause >6 million deaths annually in the world, a number similar to tobacco smoking. The effects on humans of air pollution include: asthma,* COPD, lung cancer, MI, stroke, neurodegenerative and skin disorders.**

AIR
- Increased UV light penetration via *stratospheric* ozone (O_3) deficiencies
- Particulate matter, small worst (PM_{10}, $PM_{2.5}$): e.g. smog, soot, tobacco smoke
- Organisms: bacteria and their spores, viruses
- Dust: "atmospheric, heavy or settling," e.g. derived from industry, incineration of waste, natural phenomena such as volcanic eruption
- Gases:eg CO_2/CO, sulphates, nitrous compounds, PAH , VOC.
- Increased O_3 at *ground level*.
- Heavy metals, e.g. lead
- Noise pollution
- Radioactive waste

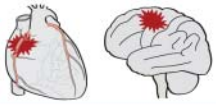


LAND
Chemical/radioactive waste e.g. heavy metals, hydrocarbons or pesticides

WATER
Chemical waste, soil waste, air pollution washed into water by rain, alteration in organisms (e.g. algal bloom in sea), plastics. Radioactive waste

Cold-induced damage

- **Hypothermia** occurs when the core temperature is <35C. **Frostbite** is localised freezing of exposed peripheries, e.g. nose, fingers
- The problems which affect resuscitation efforts are those of plasma volume depletion and alterations in ion concentration
- A cold-induced diuresis increases plasma viscosity and the blood becomes hyper-coagulable, increasing the risk of myocardial infarction and stroke on resuscitation
- Leakage of plasma occurs across damaged capillary endothelium. Hypovolaemia may cause shock if a patient is warmed suddenly, without careful monitoring and fluid and electrolyte correction
- Plasma K^+ levels rise because of the loss of integrity of the cellular Na^+/K^+ pump - this normally functions to keep intracellular K^+ levels high and Na^+ low, while the reverse is true in the extracellular fluid.
  The high plasma K^+ levels may cause cardiac arrhythmias



Heat-induced damage

Exogenous: high ambient temperatures and excessive exercise may cause **fluid and electrolyte loss and dehydration**.
Treatment is by cooling and fluid and electrolyte replacement

Mixed exogenous/endogenous: high ambient temperatures and impaired heat-losing mechanisms cause **heat stroke**.
- Example: athletes exercising in extremely hot environments
- Infants, children and the elderly, especially those taking medication such as diuretics or tranquilisers

Treatment is with cooling, fluid and electrolyte replacement – antipyretics are ineffective

Many patients develop lactic acidosis, hypocalcaemia, muscle fibre damage and myoglobinuria, which may damage renal tubules

Endogenous:
Infections cause fever due to the release of cytokines, e.g. IL-1 and TNF, which affect the temperature control centre in the hypothalamus
- Example: the drenching sweats and high fevers seen in tuberculosis and some lymphoma patients (though why this is typically at night is not clear)
- Febrile convulsions are common in children with high temperatures
- An aberrant response to anaesthetic may cause 'malignant hyperthermia'

Radiation-associated disease

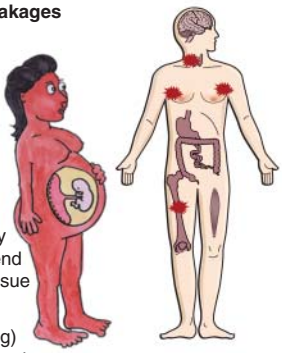
Ionizing radiation causes DNA breakages and cross-linkage.

Rapidly dividing tissues (bone marrow, gut, skin, bronchus, urinary tract) are particularly susceptible

Effects vary depending on type (α, β particles or γ , X-rays), depth of penetration, dose and host factors

Therapeutic deep X-ray radiotherapy (DXT) works because tumour cells tend to divide more rapidly than normal tissue

Radiation effects are **cumulative.** Delivering divided doses (fractionating) and converging on tumour from different angles, DXT to tumour is maximised, but normal tissue damage is minimised



Radiation effects

Immediate : High doses (e.g. 2000 rads) cause convulsion, coma and death within 1 day

Acute/subacute (hours /days-weeks)
Cerebral oedema, diarrhoea, dehydration, septicaemia (from gut breakdown), bone marrow failure

Long-term (months/years/decades) effects.
Fibrosis: strictures of small bowel, pericardial fibrosis, interstitial fibrosis of lung or kidney, spinal cord damage.
Mutation: Cancers: carcinoma (e.g. breast or thyroid), bone marrow derived cells (e.g. leukaemia, lymphoma), soft tissue (sarcomas)

Pregnancy:
In utero exposure: may cause fetal growth/mental retardation, microcephaly or hydrocephaly.
Future pregnancies in survivors: no radiation effects found

Environmental pollution

Air, soil and water are all liable to contamination (see diagram). Air pollution is a major cause of mortality and morbidity due to asthma, chronic obstructive pulmonary disease (COPD), lung cancer, myocardial infarction (MI), stroke, and neurodegenerative and skin disorders. Globally, more than 6 million annual deaths are attributed to air pollution.

Physical agents

Electrocution

Electrocution by lightning or contact with DC or AC currents from the domestic electricity supply often causes charring of the skin at the entry (e.g. hand or head) and exit (e.g. foot) points. The damage is related to the type of shock and the resistance of the tissue. Muscle tetany may render the subject unable to let go of a faulty electrical wire or socket. Electrical currents are conducted through the body best by fluids with high ion content, i.e. blood, nerves and tissue fluids. In electrically resistant tissue, such as fat, bone or tendon, the heat generated can cause severe burns and joints are often damaged. CNS injury is likely if the head is struck by lightning for example, or current passing across the body may cause cardiac arrhythmias and sudden death. Electrocution can cause respiratory arrest, seizures and rhabdomyolysis. Therapeutically, a DC shock applied to the praecordium to treat ventricular fibrillation during cardiac arrest may shock the heart back into sinus rhythm.

Extremes of temperature

Cellular homeostasis depends on temperature-sensitive enzyme reactions and the maintenance of ion concentrations within a fairly narrow range of normal values. The normal core temperature is maintained by the hypothalamus and is regulated by interleukin (IL)-1 release from macrophages and local prostaglandin production. Heat is generated by muscle and metabolic activity within the body and is lost through the skin, sweat and breath.

Excess heat: Heat exhaustion (core temperature 37–40°C with dizziness, headache, thirst, malaise and nausea) requires rehydration and cooling. Left untreated it may progress to a medical emergency, *heatstroke* (core temperature 40–42°C with severe confusion, problems with cardiac function and respiration); 42.5°C is virtually always fatal. The cause may be increased heat generation (e.g. exercise), an inability to lose heat (e.g. clothing or medication) or a disturbance of hypothalamic thermal regulatory mechanisms. The body responds by profound vasodilatation.

Burns: Cause damage by coagulating the skin and variable amounts of subcutaneous tissue. Lipid membranes melt, enzymes denature and proteins precipitate. Burns are classified as first, second or third degree according to the depth of tissue damaged and the surface area of the body affected. Plasma and tissue fluid leak from the surfaces of the burned areas and may cause hypovolaemic shock if >70% of the body surface is involved with third-degree burns. The loss of vital protein molecules in the exudate impairs the acute inflammatory response and healing. Inhalation of fire and smoke damages the respiratory tract mucosa and the alveolar walls, causing acute respiratory distress syndrome. The damaging effect of heat is utilised in radiofrequency ablation.

Cold: Hypothermia occurs when the core temperature drops to 35°C. If shivering and increased muscle activity fail to halt the fall in temperature, respiration rate, pulse, blood oxygenation and tissue perfusion decreases. Blood sludges as plasma is lost by cold-induced diuresis and leaky endothelium. The patient becomes confused, then deeply unconscious. Death is usual by 28°C.

Sudden exposure to extreme cold, as seen in frostbite, causes hypothermic damage to exposed or less well-perfused parts, such as fingers, nose or toes. The fluid in the capillaries, cells and tissues freezes and thereby increases the volume of the cells. The plasma membranes rupture, as do those of the organelles. There is gangrenous ischaemic necrosis of the extremities. Treatment is by gradual warming. Often the extent of the damage is less than initially feared, so delay hasty amputation.

Perfusion with cooled blood reduces metabolic demands and complications during cardiac transplant surgery. The transplanted heart will have been transported to the donor's hospital in a supercooled state to reduce tissue deterioration.

Radiation

Radiation causes ionisation of molecules in tissue fluid, forming free oxygen radicals (reactive oxygen species) which damage tissues. Risks are related to the type, extent and cumulative dose of radiation and the tissues exposed to it (see diagram).

Chemical agents

Exposure to strong acid or alkali ruptures cell membranes, producing cell and tissue necrosis and capillary damage with leakage of blood into tissues. The effects can mimic burns. Healing of extensive wounds is often by scarring.

Many industries generate harmful substances as by-products. Some chemicals react with cellular constituents or are altered by normal metabolic pathways to create toxic metabolites, for example:

- Conjugation with glucuronide may render a molecule safe until it is excreted by the kidney, when the glucuronide is conserved and the urinary epithelium is exposed to the toxic metabolite.
- Volatile organic compounds (VOCs), e.g. polycyclic aromatic hydrocarbons (PAHs), are generated by the petrochemical industry or by combustion of tars (e.g. soot) and also found in cigarette smoke. When converted to epoxides by cytochrome P450 they can bind and mutate DNA. Soot was linked to scrotal cancer in chimney sweeps by Percival Pott in 1775. Smoking-related PAHs are strongly linked to the development of lung cancer.
- Vinyl chloride monomers, produced during PVC manufacture, may generate chloracetaldehyde when metabolised by hepatic cytochrome P450; this can bind and mutate DNA.

Cancer treatment employs drugs that interfere with DNA replication to attack dividing cells, working on the premise that more tumour than normal cells are usually proliferating at any one time, e.g. cyclophosphamide alkylates DNA and causes nonsense mutations.

Water

Death by drowning is due to asphyxia. Diatoms from the water enter the blood and tissues. Death is four to five times faster in fresh water than salt water because the hypotonic fresh-water

solution that enters the blood via the pulmonary capillary bed causes haemodilution, with low chloride and potassium levels, and later hyperkalaemia due to red cell lysis. Sea water may be almost isotonic, although usually it is hypertonic and the blood chloride level is increased, but haemolysis does not occur, and thus resuscitation efforts have more chance of success in people rescued from the sea. People who survive near-drowning may develop pneumonitis from organisms in dirty water.

Infectious agents

In order to cause damage, organisms must evade the body's primary defences and enter the tissues (see Chapter 16).

6 The effects of tobacco, alcohol and other drugs

Effects of smoking on the body

Chemical carcinogens (>40 described)
- Tars, e.g. polycyclic aromatic hydrocarbons
- Metals, e.g. arsenic, nickel
- Tobacco-related carcinogens may show synergism, e.g. with asbestos

Smoking associated cancers
- Lung (81%)
- Larynx (77%)
- Mouth, oropharynx (60%)
- Oesophagus (60%)
- Bladder, kidney and ureter
- Pancreas
- Stomach
- Liver
- Cervix and ovary
- Bowel
- Acute myeloid leukaemia

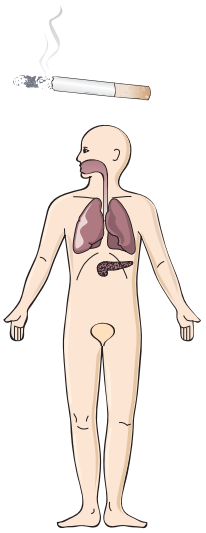
COPD

Carbon monoxide
- Binds Hb, ↓O_2 availability
- Binds myoglobin and other haem-containing proteins, e.g. cytochrome oxidases, ↓energy production.

CO and hydrogen cyanide
- Paralyze the cilia ↓clearance of particles from lungs

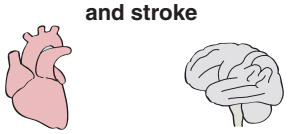
Chemicals in smoke generate reactive oxygen species

Effects may be:
- Pro-inflammatory, e.g. alveolar membrane damage in COPD
- Atherogenic, by causing endothelial cell damage
- Carcinogenic: DNA damage may cause mutations



Nicotine
- Addictive
- Predisposes to platelet adhesion and aggregation
- ↑ coronary artery flow by local vasodilatation
- ↑ cardiac output
- ↑ blood pressure by peripheral vasoconstriction,
- Directly mobilises free fatty acids from the tissues
- Chemo-attractant for PMN to lungs

Atherogenesis and likelihood of coronary artery thrombosis and stroke



Clinical note

Oral contraceptive use requires caution in smokers. They ↓ antithrombin III and ↑ fibrinogen production by the liver, ↑ platelet aggregation and blood coagulation

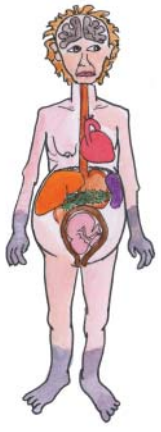
Effects of smoking during pregnancy and childhood
- Premature rupture of membranes
- ↑ risk of placenta praevia (placental implantation across the cervical canal) and abruptio placentae (premature separation of the placenta from the uterine bed)
- Carbon monoxide binds foetal Hb more avidly than adult Hb, ↓ foetal oxygenation, causing growth retardation
- Children exposed to passive smoking may develop asthma, recurrent respiratory tract and ear infections or sudden infant death syndrome

Alcohol effects

Non-neoplastic disease linked with (mainly chronic) excess alcohol ingestion
- Brain: Wernicke's encephalopathy, Korsakoff's psychosis
- Peripheral nervous system: distal sensory neuropathy 'glove and stocking' distribution
- Heart: dilated cardiomyopathy, atrial fibrillation
- Liver: fatty change, steatohepatitis, cirrhosis (see chapter 58)
- Oesophagus:
  - Bleeding varices (with cirrhosis)
  - Mallory-Weiss tear (acute effect after vomiting)
- Stomach: alcoholic gastritis (acute effect)

Effects of alcohol on developing foetus

Foetal alcohol syndrome can develop with ≤ 1 unit of alcohol/day, causing developmental abnormalities in brain, heart, bone and genitourinary systems



Alcohol associated cancers
- Bowel
- Breast
- Mouth, throat, oesophagus (squamous carcinoma)
- Liver
- Larynx

Acetaldehyde, an intermediary product in alcohol metabolism, has been shown to mutate stem cells in mouse experiments.

Other alcohol-associated problems
- Social withdrawal
- Violence
- Traumatic injury (road or other accidents, domestic abuse)
- Financial problems
- Psychiatric disorders

Tobacco

Tobacco is damaging when smoked either directly or indirectly ('passive smoking'), but also has deleterious effects when chewed, or inhaled as snuff. It is addictive because of pleasurable effects such as increased feeling of well-being and alertness and decreased appetite. It has effects on children, the unborn fetus and on pregnancy itself. Long-term use causes cancer (smoking is considered a significant causative factor in 86% of lung cancers and 19% of all UK cancers), cardiovascular disease and respiratory disease.

Tobacco smoke is absorbed into the blood via the alveolar capillaries or via the gastrointestinal tract in swallowed sputum. It has a direct effect on the mucous membranes lining the oropharynx, respiratory tract and oesophagus. The toxic effects of tobacco smoke are due to both gaseous and particulate agents.

Gaseous elements

- Carbon monoxide (CO) shows 200 times oxygen's affinity for haemoglobin and reduces oxygen availability to the tissues.
- CO or hydrogen cyanide may paralyse the cilia, impairing the removal of inhaled particles from the respiratory tract.

Particulate elements

Nicotine

- Nicotine stimulates nicotine receptors in the brain to cause addiction.
- It increases blood pressure by direct catecholaminergic effects.
- It mobilises free fatty acids from the tissues, important in atherogenesis.
- Nicotine predisposes to platelet adhesion and aggregation, increasing the risk of coronary arterial thrombosis and myocardial infarction or cardiac arrhythmia.
- It is a chemoattractant, luring polymorphs and macrophages to the alveolar space.

Chemical carcinogens

- Over 40 smoke-related carcinogens are known, chief of which are the polycyclic aromatic hydrocarbons (PAHs), and also carcinogenic metals such as arsenic and nickel.
- Smoking is linked to cancers of the respiratory tract, oropharynx, oesophagus, bladder and probably the pancreas.
- Tobacco-related carcinogens may act synergistically with each other, or with non-smoking-related carcinogens.
- Tobacco smoke contains reactive oxygen species (ROS), also known as free radicals.

Irritant substances

- Cancer-promoting agents that stimulate cell turnover, increasing the risk of mutation induced by carcinogens, include acetaldehyde and phenol.
- These cause chronic obstructive pulmonary disease (COPD; Chapter 45) by inducing inflammation in the lung and respiratory tree, which can damage the delicate alveolar walls and cause emphysema or stimulate mucous cells to increase mucin secretion, which is difficult to clear if ciliary function is impaired, resulting in chronic bronchitis.
- ROS stimulate the acute inflammatory response and cause further damage.

Combined effects

Tobacco smoke may synergise with other agents to multiply the amount of damage either would cause independently. Examples include the following.

- Occupational-related asthma or COPD, e.g. silicosis in coal miners, dust from grain in farm workers, or fumes from welding and asbestosis.
- Cancer related to occupational exposure, e.g. blue asbestos may cause primary lung cancer or mesothelioma (cancer of the pleura) but the risks are increased 20-fold in smokers.

Alcohol

Ethanol (ethyl alcohol)

Alcohol affects many organs and systems, as shown in the diagram. Binge drinking (one-off consumption of large quantities) is linked to cardiac damage. Chronic consumption of more than 21 units/week (men) and 14 units/week (women) causes liver damage in at least 50% and increases the risk of dementia, hypertension and breast and other cancers. Women have less alcohol dehydrogenase in their gastric wall and thus cannot metabolise as much alcohol as men. One unit equates to one measure of spirits, one small glass of wine or half a pint (250 mL) of normal strength beer.

Proponents of moderate alcohol drinking point to studies into the incidence of cardiovascular disease and dementia; the graph of alcohol consumption versus disease incidence is a 'J'-curve indicating that these diseases are seen less in people who consume roughly 7 units per week, particularly red wine, than in abstainers. Anti-alcohol campaigners suggest that this does not take into account the possible pre-existing health problems making some abstain.

It is illegal to drive in the UK with blood alcohol levels above 80 mg/dL. Unaccustomed drinkers are unconscious at 200 mg/dL; some chronic drinkers can tolerate 700 mg/dL, due to the induction of liver enzymes. Other drugs may compete with alcohol for these paths, rendering their effects unpredictable.

Ethanol directly damages cell membranes, e.g. skeletal muscle, cardiac muscle (ventricles dilate) and other sites. Hepatotoxic effects are probably from cytokine release by activated Kupffer cells, compounded in chronic alcoholics by amino acid deficiencies and cardiac failure. The metabolism of alcohol and its wider effects on the liver are discussed in Chapter 61.

Other alcohols

- *Methanol (methyl alcohol)*: this is very slowly metabolised over many hours/days by the same pathway as alcohol, with the highly toxic end-product of formic acid. The initial sensation of inebriation is similar to ethanol, but the meths drinker develops a severe metabolic acidosis, vomiting, dizziness, blurred vision and blindness and may die from respiratory depression.
- *Ethylene glycol*: this is the main constituent of antifreeze, and reacts with metals in the body to form toxic aldehyde products. Patients who survive the initial insult often develop renal calcium oxalate stones and acute tubular necrosis.

Ironically, the treatment of methanol and ethylene glycol poisoning is ethanol, which competes for the metabolic pathways, giving the body more time to clear metabolites before toxic effects occur.

General observations regarding common therapeutic and addictive drugs

The mechanisms by which drugs produce toxic effects are numerous and may be direct effects of the drug, or indirect due to its metabolites. Some drugs cause predictable dose-related effects, whilst others are unpredictable, only affecting some people. A drug's pharmacological effects may be directly harmful, e.g. bone marrow suppression by chemotherapeutic agents, or it may have harmful side effects, e.g. diarrhoea induced by erythromycin. Recreational drugs can produce physical and/or psychological dependence, which can induce harmful patterns of behaviour that have deleterious psychological, physical and social consequences.

A drug's metabolites may be harmful. Most drug metabolism occurs in the liver. The basic aim of metabolism is to render the drug inactive and water soluble, the latter to facilitate excretion in the urine or bile, a feat achieved by a set of enzymes that conjugate the drug by adding chemical groups to it. These include hydroxylation (cytochrome P450 system), glucuronidation and conjugation with glutathione. These enzymes show genetic polymorphism and can be induced or inhibited by other drugs. Paracetamol overdose is a very important example of a drug that is rendered toxic by metabolism.

7 Nutritional disorders

Vitamins	Source	Disease caused by deficiency
Water-soluble		
B1 thiamine	Grains, liver, eggs, brown rice, vegetables	Beriberi
B2 riboflavin	Dairy, bananas, green beans, asparagus	Glossitis, angular stomatitis
B3 niacin	Meat, fish, eggs, vegetables, mushrooms, nuts	Pellagra
B5 pantothenic acid	Meat, grain, broccoli, avocados	Paraesthesiae
B6 pyridoxine	Meat, dairy	Peripheral neuropathy, anaemia
B7 biotin	Meat, eggs, dairy	Dermatitis, enteritis
Folate (B9)	Leafy vegetables	Megaloblastic anaemia; neural tube defects if mother deficient
B12 cyanocobalamin	Meat, eggs, liver	Megaloblastic anaemia, spinal cord degeneration
C ascorbic acid	Fresh fruit (particularly citrus), liver	Scurvy
Fat-soluble		
A retinol	Liver, cod liver oil, fish, dairy; spinach; orange or yellow vegetables or fruits	Night blindness, hyperkeratosis keratomalacia
D calciferol	Cod liver oil, sardines, eggs, some mushrooms	Rickets/osteomalacia
E tocopherol	Fruits, nuts, seeds, vegetables, oils	Rare (haemolytic anaemia in infants)
K phylloquinone	Egg yolks, leafy green vegetables, liver	Coagulopathy

The seven essential dietary substances
- Water
- Carbohydrates: energy
- Proteins (9 'essential' amino acids)
- Fat
- Vitamins
- Minerals
- Fibre (*insoluble, soluble*)

Body mass index (BMI) kg/m^2:
To calculate: Weight in kg/(Height in m)^2
Underweight <19.9
Normal 20–24.9
Overweight 25–29.9
Obese>30

Waist/hip ratio (WHR)
Estimates visceral fat deposition, which is more metabolically active than subcutaneous.
Circumference of waist/circumference of hips should be <0.9 men, <0.85 women

Under-nutrition

Marasmus
- Severe protein-calorie deficiency, body weight < 60% of normal for age and height
- Severe growth retardation
- Head appears huge because the rest of the body is emaciated, particularly the extremities, because of the extreme depletion of the subcutaneous fat and loss of skeletal muscle bulk
- Muscle is catabolised in order to maintain the serum albumin level, so oedema is not a feature (see fluid compartments; Chapter 2)

Kwashiorkor
- Weight 60–80% of normal (deficiency of protein, but carbohydrate sufficient)
- Skeletal muscle bulk appears normal; subcutaneous fat stores are maintained
- Black hair may appear red or alternating stripes of hyper- and hypo-pigmentation may be seen, and tufts of hair may fall out
- Flaky desquamation of skin may occur in patches
- Oedema in dependent parts due to low plasma albumin
- Chubby but apathetic, with no appetite
- Liver enlargement with severe fatty change
- Anaemia common, iron deficiency or mixed picture
- Thymic and lymphoid atrophy compromise immunity
- Small bowel undergoes villous atrophy. This adds malabsorption to the list of problems, and there may be secondary as well as primary deficiencies, often of vitamins

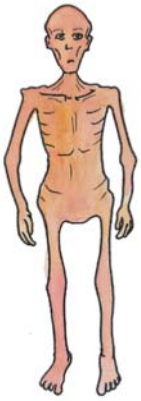
Over-nutrition

Obesity
- BMI >30, ↑ WHR (apple- worse than pear-shaped physique). Fat is metabolically active; excess fat is pro-inflammatory.
- ↑ cardiovascular disease: ↑BP, atherosclerosis, MI and stroke
- ↑ diabetes mellitus
- ↑ fatty liver, which can cause steatohepatitis and cirrhosis
- ↑ weight–associated problems: osteoarthritis, gastro-oesophageal reflux, sleep apnoea
- ↑ cancers of bowel, breast, endometrium, oesophagus/cardia of stomach, ovary, thyroid, pancreas and gallbladder.

Metabolic syndrome - three or more of the following:
- Insulin intolerance/diabetes mellitus
- Hypertension
- High LDL/TG
- Low HDL
- Obesity (BMI <30 or high WHR)

Nutrition cannot be utilized adequately

Cachexia
- Catabolism of skeletal muscle and visceral and subcutaneous fat stores leads to wasting, especially in deltoid muscles and upper limb girdle subcutaneous tissues
- Cytokines such as TNF, IL-1 and IL-6 implicated, released by some malignant tumours and in chronic inflammatory states such as tuberculosis and AIDS
- Dietary supplementation unsuccessful



Carbohydrates, proteins and fats are sources of both energy and structural materials, although proteins have predominantly structural roles and carbohydrates are mainly an energy source. Twenty amino acids are used in the body's proteins, of which nine cannot be synthesised and are therefore termed essential. The remaining 11 can be generated from the nine essential amino acids if they are not provided by the diet.

Vitamins and minerals do not provide energy but have specific roles in metabolic pathways (e.g. vitamin C and collagen synthesis), as prosthetic groups (e.g. iron in haemoglobin) and as substrates for vital molecules (e.g. vitamin A and rhodopsin).

Fibre is not absorbed from the gut, but facilitates peristalsis and the formation of stools and nourishes the gut microbiota. *Insoluble fibre* (e.g. plant cellulose) attracts water to the stool, softening it and increasing its bulk. *Soluble fibre* (e.g. pectins in fruit, β-glucans in oats) dissolves in water, forming a gel which lines the gut. This slows the absorption of sugars (with a beneficial effect on blood insulin levels) and binds cholesterol and bile salts, which are then excreted (this lowers blood LDL and increases HDL).

Nutritional deficiency

Primary nutritional deficiency is due to a decrease in food intake where this reduction is not due to an underlying illness. The decrease may be generalised, as in marasmus and kwashiorkor, or selective, such as specific vitamin deficiencies or malabsorptive syndromes. The growth requirements of young children, pregnant women and adolescents render them more susceptible to the more gross manifestations of nutritional deficiencies than adults.

Secondary causes of selective or global nutritional deficiency include reduced food intake secondary to another condition (e.g. chronic alcoholism or cancer cachexia) or defective absorption of food (see malabsorption disorders, Chapter 52) and psychiatric disorders of appetite and eating behaviour, anorexia and bulimia.

Protein energy malnutrition

This term is employed most commonly in relation to marasmus and kwashiorkor. Patients with severe malnutrition often have deficient immunity due to lack of dietary protein substrates for immune molecules and may have one or more infections at presentation. The cytokine release and energy demands resulting from the inflammatory response may compromise the patient's status further.

- *Marasmus*: marked protein and calorie deficiency and severe growth retardation.
- *Kwashiorkor*: a particular problem in African and Southeast Asian children who are weaned from the breast when a new baby arrives and for whom the only available diet is composed almost exclusively of carbohydrate. The absence of essential amino acids prevents new protein synthesis by the liver.

Cachexia

This is a catabolic process resulting from chronic disease such as malignancy (e.g. carcinoma of stomach, pancreas and bronchus) or infection (e.g. HIV/AIDS or tuberculosis). The patient is emaciated due to *loss of body fat* around the arms, shoulders, chest wall and often the hand, and a marked *reduction in skeletal muscle*, particularly in the deltoid and quadriceps. Dependent oedema can occur.

Cachexia is driven by cytokines such as tumour necrosis factor (TNF) and interferons (particularly IL-1 and IL-6), secreted by or in response to the underlying condition. Current treatments centre on manipulating the catabolic pathways activated by these cytokines.

Obesity

Obesity, defined by a body mass index (BMI) of over 30 kg/m^2 or by an increased waist/hip ratio, can cause health problems in the cardiovascular, endocrine, gastrointestinal and many other systems and increase cancer risk (see diagram). Obesity is now a global problem, affecting all ages. Cheap low-fibre, high-calorie carbohydrate and trans- and saturated fat-rich processed food and a more sedentary lifestyle are implicated in obesity. Genetic factors may predispose to weight gain, but epigenetic factors (the effect of environmental factors on gene expression) probably play a larger role. The gut microbiome and dietary fibre can modulate the risk of diabetes mellitus (see Chapter 20).

Metabolic syndrome

This tends to occur in inactive, middle-aged or older people (>45 years). It is a complex, pro-atherogenic, low-grade inflammatory syndrome characterised by any three of visceral obesity, hyperlipidaemia, diabetes mellitus, non-alcoholic fatty liver disease, hypertension or atherosclerosis. Adipose tissue and its tissue macrophages are metabolically active, e.g. *adipokines* from fat modulate inflammation, insulin resistance and appetite (*leptins* are proinflammatory and *adiponectins* anti-inflammatory).

Inflammation and immunity