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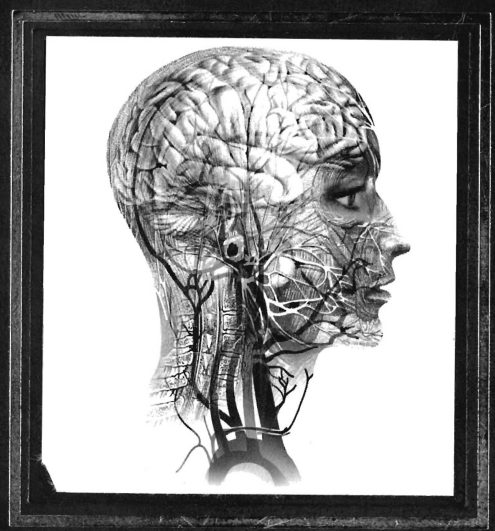
Scott-Brown's Otorhinolaryngology, Head and Neck Surgery

VOLUME 1



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Scott-Brown's Otorhinolaryngology, Head and Neck Surgery

Scott-Brown's Otorhinolaryngology, Head and Neck Surgery 7th edition

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Preface

Fifty-five years have passed since the first edition of *Scott-Brown's Otorhinolaryngology: Head and Neck Surgery* was published. Many otorhinolaryngologists have read at least one edition, committed it to memory and passed their specialist examinations because of it. All will have kept referring to it throughout their careers and remember it with affection. Looking back it is apparent that a radical change in structure and format has taken place every 15 to 20 years. It is 20 years since Alan Kerr made the last radical change with the publication of the 5th edition, 20 years that have seen an information technology explosion. The internet, on-line libraries, e-delivery of journals and increasingly books, computerised search engines, CD-ROMs, DVDs, digital photography; the list goes on. These technological advances have transformed medical education, influenced significantly the way the current generation learns and the methods by which their competencies and knowledge are assessed. Certainly sufficient time has elapsed for *Scott-Brown* to evolve dramatically once more. This edition has been completely re-written. It bears little resemblance to its predecessors other than by title, and in its philosophy to provide a complete resume of the knowledge base that underpins modern ORL practice and which will guide clinicians in their everyday patient care for years to come. The number of chapters has almost doubled, with large topics dissected into more digestible parts. This reflects the expansion of our specialty such that it is now a group of subspecialties linked by the common thread, each concerned with, and committed to, the care of patients with disorders of the head and neck.

Our authors are the leading experts in their respective fields of interest and have been selected from all over the world. Almost all the text is illustrated in colour and it comes with its own CD-ROM, containing all the text and illustrations in an accessible and searchable form, with references linked to PubMed.

So what else could the trainee or practising otorhinolaryngologist want from the definitive reference to the field at the beginning of the new millennium? Quite simply, the level of evidence for the advice we offer and the practice we undertake. Nowadays specialties need to define best clinical practice, if only to guide and remind health care providers of their duty to their patients to practice in accordance with accepted evidence and to strive for excellence in clinical standards at all times. Surgeons also need to know how their actions might be viewed by the courts and the areas of practice that are currently exercising the legal profession. This edition has tried to provide that information.

It has not been an easy task for our contributors, some of whom were not writing in their mother tongue. That they were able to write to a structured format was much to their credit. I was fortunate to recruit, and am extremely grateful to, my team of section editors all of whom worked tirelessly with a common purpose. George G Browning, Martin J Burton, Ray Clarke, John Hibbert, Nicholas S Jones, Valerie J Lund, Linda M Luxon and John C Watkinson represent some of the very best and most respected clinicians in the United Kingdom, each one an international authority, each one with a heavy professional commitment. Alan Kerr's advice and encouragement throughout was always welcome and extremely useful. Marcelle McNamara came to my aid and assistance numerous times during the project. She gave tirelessly of her time and energy during a very serious illness, writing chapters and putting others into format and a more readable form. She was an example and inspiration throughout.

The creation of this edition has also been an interesting experience for the publishing staff. During a lengthy period of gestation, this text has changed ownership several times as the publishing houses traded and realigned their lists. Without the drive and perseverance of Zelah Pengilley and Jo Koster from Hodder Education it would surely have fallen by the wayside. Words cannot express my gratitude to them adequately. Understanding when clinical work overwhelmed me, they hid their frustrations over slow progress or irritatingly incomplete manuscripts. They buoyed us all up when the end seemed so far away.

Sadly, some of our contributors will never see their chapters in print as they have died during the preparation of this text. Some had long, unpleasant illnesses but wrote despite them. Others were cut down unexpectedly in their prime but have now left a legacy, and a few were my close friends and colleagues. I am proud to have my name linked permanently through this publication with Michael Baser, Roderick Cawson, Susanna Leighton,

William Owen, Robert Sanderson and Antonio Vignola. We hope that their families will draw some comfort also by seeing their loved ones live on in this book.

Finally, there are four very special people whose constant love and affection drives me on through life. They are of course my wife, Ann, and our children, Andrew, Clare and Mark. They too will breathe a deep sigh of relief with the publication of this text and I thank them with all my heart.

Michael Gleeson
September 2007

How to use this book

This new edition of *Scott-Brown's Otorhinolaryngology, Head and Neck Surgery* incorporates some special features to aid the readers' understanding and navigation of the text. These are described below.

SEARCH STRATEGY

The majority of the chapters feature a search strategy indicating the key words used by the author when conducting their literature review in order to prepare the chapter, so that the reader can repeat and develop the search.

EVIDENCE SCORING

For the major sections in each chapter, the authors have used a hierarchical system to indicate the level of evidence supporting their statements. This is shown in the text in the form [***], with the number of stars indicating the level of evidence. The key to this system is shown in the table below.

Level	Category of evidence
****	Systematic reviews, meta-analyses of randomized controlled trials and randomized controlled trials
***	Non-randomised studies
**	Observational or non-experimental studies
*	Expert opinion

Where no level is shown, the quality of supporting evidence, if any exists, is of low grade only (for example, case reports, clinical experience etc.). For more information on evidence scoring, please refer to Chapter 304, Evidence-based medicine; and 305 Critical appraisal skills.

CLINICAL RECOMMENDATIONS

The authors have indicated the basis on which they have made clinical recommendations by grading them according to the level of the supporting evidence. This is shown in the text in the form [Grade A], with the grade indicating the level of evidence supporting the recommendation. The key to this system is shown in the table below.

Grade	Nature of supporting evidence
A	Recommendation based on evidence from meta-analyses of randomized controlled trails
B	Recommendation based on evidence from high quality case-controlled or cohort studies
C	Recommendation based on evidence from low quality case-controlled or cohort studies
D	Recommendation based on evidence from clinical series or expert opinion

Recommendations are graded where the author is satisfied that the literature supports such a grading; otherwise a grading may not be given.

REFERENCE ANNOTATION

The reference lists are annotated with an asterisk, where appropriate, to guide readers to key primary papers and major review articles. We hope that this feature will render the lists of references more useful to the reader and will encourage self-directed learning among both trainees and practicing physicians.

Abbreviations

2,3DPG	2,3-diphosphoglycerate
2D	two-dimensional
3,4-DAP	3,4-diaminopyridine
3D	three-dimensional
5-FdUMP	5-fluoro-2 deoxyuridine monophophate
5-FU	5-fluorouracil
5-FUMP	5-fluorouridine monophosphate
5-HT	5-hydroxytryptamine
6MP	6-Mercaptopurine
18-FDG	2-18-fluoro-2-deoxy-D-glucose
A	adenine; or anterior
AABR	automated auditory brainstem response
AAHL	age-associated hearing loss
AAOHNS	American Academy of Otolaryngologists/ Head and Neck Surgeons
AAV	adeno-associated virus
ABC	aspiration biopsy cytology
ABEP	auditory nerve and brainstem evoked potential
ABG	air–bone gap
ABI	auditory brainstem implant
ABLB	alternate binaural loudness balance
ABPA	allergic bronchopulmonary aspergillosis
ABR	auditory brainstem response; or acoustic brainstem evoked response
ABRS	acute bacterial rhinosinusitis
AC	air conduction; or alternating coupled
ACC	adenoid cystic carcinoma; or American College of Cardiology
ACE	angiotensin-converting enzyme
ACF	anterior cranial fossa
ACh	Acetylcholine
AchR	acetyl choline receptor
ACT	Aid for Children with Tracheostomies
ACTH	adrenocorticotropic hormone
A/D	analogue-to-digital
AD	Alzheimer's disease
ADA	adenosine deaminase
ADAM-33	A disintegrin and metalloprotease 33κ
ADCC	antibody-dependent cellular cytotoxicity
ADH	antidiuretic hormone
ADHD	attention deficit hyperactivity disorder
ADR	adverse drug reaction
Ad-VEGF	adenovirus-encoding vascular endothelial growth factor
AECRS	acute exacerbation of chronic rhinosinusitis
AED	aerodynamic equivalent diameter
AEDS	atopic eczema dermatitis syndrome
AEF	auditory-evoked cortical magnetic field
AF	atrial fibrillation; or anterior fontanelle
AFB	acid-fast bacilli
AFRS	allergic fungal rhinosinusitis
AgNOR	silver staining nucleolar organizer region
AHA	American Heart Association
AHCPR	Agency for Health Care Policy and Research (USA)
AHI	apnoea/hypopnoea index
AI	apoptotic index
AICA	anterior inferior cerebellar artery
AIDS	acquired immunodeficiency syndrome
AIRE	autoimmune regulator gene
AJCC	American Joint Committee on Cancer
ALD	assistive listening device
ALEP	auditory long-latency (or late) evoked potential
ALL	acute lymphoblastic leukaemia
α2β2	two α and two β globin chains
α2δ2	HbA2
α2γ2	foetal haemoglobin
ALPS	autoimmune lymphoproliferative syndrome
ALS	amyotrophic lateral sclerosis
ALT	alternative lengthening of telomere; or alternating chemoradiotherapy
ALTB	acute laryngotracheobronchitis
ALTE	apparent life-threatening event
AML	acute myeloid leukaemia
AN	acoustic neuroma; or auditory neuropathy; or audiovestibular nerve
ANA	anti-nuclear antibody
AN/AD	auditory neuropathy/auditory dyssynchrony
ANCA	antineutrophil cytoplasmic antibody
AND	allow a natural death
ANUG	acute necrotizing ulcerative gingivitis
AOAE	automated otoacoustic emission
AoCD	anaemia of chronic disease
AOM	acute otitis media

AON	anterior olfactory nucleus
AP	anterior–posterior; or action potential
APB	ALT-associated promyelocytic leukaemia body
APC	antigen presenting cell; or activated protein C; or argon plasma coagulation; or adenomatous polyposis coli
APD	auditory processing disorder
APECED	autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy
APHAB	Abbreviated Profile of Hearing Aid Benefit
APL	anti-phospholipid
APMET	aggressive papillary middle ear tumour
APQ	amplitude perturbation quotient
APTT	activated partial thromboplastin time
APUD	amine precursor uptake and decarboxylation
ARF	acute renal failure
ARIA	allergic rhinitis and its impact on asthma
ARR	absolute risk reduction
ARS	acute rhinosinusitis
ART	advanced rotating tomograph; or antiretroviral therapy
ARTA	age-related typical audiogram
ASA	aspirin-induced asthma; or aspirin-sensitive asthma; or American Society of Anesthesiologists
a-SCC	anterior semicircular canal
ASIC	application specific integrated circuit
ASL	American sign language; or arterial spin labelling
ASPO	American Society of Pediatric Otolaryngologists
ASSR	auditory steady state response
AST	arterial spin tagging
AT	ataxia telangiectasia; or auditory therapy or training
ATD	ascending tract of Deiters
ATIII	antithrombin III
ATN	auriculotemporal nerve
ATP	adenosine triphosphate
ATRA	all-trans retinoic acid
AUC	area under the curve
AV	apical vesicles; or arteriovenous
AVCN	anteroventral cochlear nuclei
AVM	arteriovenous malformation
aVOR	angular VOR
AZT	3′azido3′deoxythymidone zidovudine; or azothiaprine
BAC	bacterial artificial chromosome
BACDA	British Association of Community Doctors in Audiology
BADS	British Association of Day Surgery
BAES	British Association of Endocrine Surgeons
BAHA	bone-anchored hearing aid
BAHNO	British Association of Head and Neck Oncologists
BAO-HNS	British Association of Otorhinolaryngologists – Head and Neck Surgeons
BAPO	British Association for Paediatric Otolaryngology
BCC	basal cell carcinoma
BCG	Bacillus Calmette–Guérin
BCHA	bone conductor hearing aid
BCSH	British Committee for Standards in Haematology
BDP	beclomethasone dipropionate
BE	bulla ethmoidalis
BF	biofeedback
BFU-E	burst-forming unit erythroid
BiPAP	bilevel positive airway pressure
BIPP	bismuth and iodoform paraffin paste
BL	Burkitt's lymphoma
BMA	British Medical Association
BMI	body mass index
BMP	bone morphogenetic protein; or bone morphogenic protein
BMS	burning mouth syndrome
BMT/SCT	bone marrow stem cell transplantation
BOA	behavioural observation audiometry
BOLD	blood oxygenation level-dependent
BOR	brachio-oto-renal
BP	blood pressure
BPD	bronchopulmonary dysplasia
BPPV	benign positional paroxysmal vertigo
BPV	benign paroxysmal vertigo; or benign positional vertigo
BS	Behçet's syndrome
BSE	bedside swallowing examination; or bovine spongiform encephalopathy
BSL	British sign language
BTE	behind the ear
BVF	bilateral vestibular failure
C	cytosine
CAD	caspase-activated DNase
CADCAM	computer-aided design, computer-aided manufacture
CAGE	cerebral air gas embolism
cAMP	3′,5′-monophosphate
CANS	central auditory nervous system
CAP	compound action potential; or category of auditory performance
CAPD	central auditory processing disorder
CaR	calcium sensing receptor
CAS	computer-assisted surgery
CATCH-22	cardiac defects, abnormal facies, thymic hypoplasia, cleft palate and hypocalcaemia-22
CB	concha bullosa; or critical bandwidth
CBF	ciliary beat frequency

CBT	cognitive-behavioural therapy
CCA	common carotid artery
CCDU	colour-coded duplex ultrasonography
CCR	chemokine receptor
CCW	counter-clockwise
CD	cluster of differentiation; or colloid droplets; or compact disk
CDA	cold dry air
CDC	Centers for Disease Control and Prevention
CDK	cyclin-dependent kinase
CDP	computerized dynamic posturography
CE-CT	contrast-enhanced computed tomography
CEA	carcinoembryonic antigen
CEPOD	Confidential Enquiry into Perioperative Deaths
CER	control event rate
CERA	cortical evoked response audiometry
CEVMP	click-evoked vestibular myogenic potential
CF	cystic fibrosis; or characteristic frequency
CFD	colour-flow duplex Doppler
CFR	craniofacial resection
CFTR	cystic fibrosis transmembrane conductance regulator
CFU	colony-forming unit
CFU-GM	colony-forming unit, granulocyte-macrophage
CFU-Mk	colony-forming unit, megakaryocyte
CG	clinical governance
CGD	chronic granulomatous disease
CGH	comparative genomic hybridization
CGRP	calcitonin gene-related peptide
CGST	Clinical Governance Support Team
CHARGE	coloboma, heart defects, atresia choanae, retardation of growth, genital anomalies and ear abnormalities
CHART	continuous, hyperfractionated, accelerated radiotherapy
CHI	Commission for Healthcare Improvement (UK)
CI	cochlear implant; or cardiac index; or confidence interval; or concha inferior
CID	Central Institute for the Deaf
CJD	Creutzfeldt–Jakob disease
CL	cleft lip
CL/P	cleft lip with or without cleft palate
CLL	chronic lymphatic leukaemia; or chronic lymphocytic leukaemia
CM	concha media; or cochlear microphonic; or cricothyroid muscle
CMAP	compound muscle action potential
CME	continuing medical education
CMI	cell-mediated immunity
CML	chronic myeloid leukaemia
CMT	Charcot-Marie-Tooth
CMV	*Cytomegalovirus*
CN	cranial nerve; or cochlear nuclei; or cochlear nerve
CNO	chronic nasal obstruction
CNS	central nervous system
CO_2	carbon dioxide
COAD	chronic obstructive airway disease
COM	chronic otitis media
COPD	chronic obstructive pulmonary disease
COR	conditioned orientation reflex
COSI	Client Oriented Scale of Improvement
COX-2	cyclo-oxygenase 2
CP	cleft palate
CPA	cerebellopontine angle
CPAP	continuous positive airway pressure
CPD	citrate phosphate dextrose; or continuing professional development
CPG	central pattern generator
CPO	cleft palate only
CPPIH	Commission for Patient and Public Involvement in Health (UK)
CPR	cardiopulmonary resuscitation
CQI	continuous quality improvement
CREST	calcinosis, Raynaud's, oesophageal involvement, sclerodactyly, telangiectasis
CRF	corticotrophin-releasing factor
CRH	corticotropin-releasing hormone
CROS	contralateral routing of signal or sound
CRP	C-reactive protein; or canalith repositioning procedure
CRRT	continous renal replacement therapy
CRS	chronic rhinosinusitis; or congenital rubella syndrome
CRSS	chronic rhinosinusitis
CS	corticosteroid
CSCI	Commission for Social Care Inspection (UK)
CSF	cerebrospinal fluid
CSM	Committee on Safety of Medicines
CSOM	chronic suppurative otitis media
CT	computed tomography
CTA	composite tissue allograft
CTL	cytotoxic T-lymphocyte
CTLA	cytotoxic T-lymphocyte-associated antigen
CTLL	cytotoxic T-lymphocyte leukaemic
CTM	cricothyroid membrane
cTNM	clinical tumour, nodes, metastases
CTR	cricotracheal resection
CTZ	chemoreceptor trigger zone
Cu-ATSM	Cu(II)-diacetyl-bis-N4-methylthiosemicarbozone
CUP	carcinoma of unknown primary origin
CUSA	cavitational ultrasonic surgical aspirator
CVA	cerebrovascular accident
CVD	central vestibular disorder
CVI	common variable immunodeficiency
CVP	central venous pressure
CW	clockwise
CXR	chest x-ray
CYP	cytochrome P450

DACH	diaminocyclohexane
DAHANCA	Danish Head and Neck Cancer Study
DAHNO	Data for Head and Neck Oncology (UK)
dB	decibel
dB SPL	decibel sound pressure level
DBPCFC	double-blind placebo-controlled food challenge
DCIA	deep circumflex iliac artery
DCN	dorsal cochlear nucleus
DCR	dacryocystorhinostomy
DD	death domain
DDHS	Direct Drive Hearing System
DFF	DNA fragmentation factor
DFN3	deafness type 3
DFO-H	deferoxamine-hespan
DHA-S	dehydroepiandrosterone sulphate
DHE	dihaematoporphyrinether
DHI	dizziness handicap inventory
DHTR	delayed haemolytic transfusion reaction
DIC	disseminated intravascular coagulation
DIEP	deep inferior epigastric perforator
DILS	diffuse infiltrated lymphocytosis syndrome
DIT	diiodotyrosine
DLE	discoid lupus erythematosus
DM	diabetes mellitus
DMD	Duchenne muscular dystrophy
DMSA	dimercapto succinic acid
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DNAR	do not attempt resuscitation
DNL	nasolacrimal duct
DNR	do not resuscitate
dNTP	deoxynucleoside triphosphate
DP	directional preponderance
DPA	Data Protection Act (UK)
DPOAE	distortion product otoacoustic emission
DR	death receptor; or drug resistance
DRS	Dysphagia Research Society
DSA	digital subtraction angiography
DSI	Dysphonia Symptom Index
DSL	desired sensation level
DTD	DT-diaphorase
DTIC	dimethyl triazeno imidazole carboxamide
dTMP	deoxythymidine monophosphate
DTPA	diethylene triamine pentacetic acid
dUMP	deoxyuridine monophophase
DVB	degree of voice break
DVLA	Driver and Vehicle Licensing Authority (UK)
DVN	descending vestibular nuclei
DVT	deep vein thrombosis
DWI	diffusion weighted image
EA	episodic ataxia; or early antigen
EAACI	European Academy of Allergology and Clinical Immunology
EAC	external auditory canal; or external acoustic canal
EAL	ethmoidal artery ligation
EAM	external auditory meatus
EB	epidermolysis bullosa
EBM	evidence-based medicine
EBNA	Epstein–Barr virus-associated nuclear antigen
EBP	evidence-based practice
EBV	Epstein–Barr virus
EC	embryonic carcinoma
ECA	external carotid artery
ECAL	external carotid artery ligation
ECAP	electrically evoked compound action potential
ECC	extracorporeal circuit
ECG	electrocardiogram
ECM	extracellular matrix
ECMO	extracorporeal membrane oxygenation
EcochG	electrocochleography
ECog	electrocochleogram
ECOG	Eastern Cooperative Oncology Group (USA)
ECP	eosinophil cationic protein
ECR	extracapsular rupture
EDGT	early goal-directed therapy
EDN	eosinophil-derived neurotoxin
EDS	excessive daytime sleepiness
EDTA	ethylenediaminetetraacetic acid
EDV	end diastolic velocity
EE	external frontoethmoidectomy
EEG	electroencephalography; or electroencephalogram
EER	experimental event rate
EFS	event-free survival
EG	embryonic germ
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EIA	enzyme immunoassay
ELDCR	endonasal laser dacryocystorhinostomy
ELG	electrolaryngography
ELISA	enzyme-linked immunosorbent assay
ELST	endolymphatic sac tumour
EM	erythema multiforme
EMEA	European Agency for the Evaluation of Medicinal Products
EMG	electromyography
EMI	elective mucosal irradiation
EN	enteral nutrition
ENA	extra nuclear antigen
ENG	electronystagmography
ENoG	electroneurography
ENT	ear, nose and throat
EOG	electroolfactogram; or electrooculography
EORTC	European Organisation for Research and Treatment of Cancer
EP	endolymphatic potential

EPO	erythropoietin
EQ-5D	EuroQol
ER	enhancement ratio; or endoplasmic reticulum
ERB	equivalent rectangular bandwidth
ERM	ezrin, radixin, moesin
ERP	event-related potential
ERT	external radiotherapy
Er:YAG	erbium:yttrium-aluminium-garnet
ES	embryonic stem; or endolymphatic sac
ESPAL	endonasal ligation of the sphenopalatine artery
ESR	erythrocyte sedimentation rate
ESS	endoscopic sinus surgery; or Epworth Sleepiness Scale
ET	essential thrombocytosis; or endotracheal tube
ET-1	endothelin-1
ETT	endotracheal tube
EU	European Union
EUA	examination under anaesthesia
EVAS	enlarged vestibular aqueduct syndrome
EXIT	extrauterine intrapartum treatment
F_0	fundamental frequency
FAAF	four alternative auditory feature
Fab	fragment antigen binding
FACS	fluorescence-activated cell sorter
FACT	functional assessment of cancer therapy
FAMM	facial artery myomucosal flap
Fas-L	Fas ligand
FBC	full blood count
Fc	fragment crystallizable
FD	fibrous dysplasia
FDA	Food and Drug Administration (USA)
FDG	fluorodeoxyglucose; or 2-[^{18}F] fluoro-2-deoxy-D-glucose; or F18-fluoro-2-deoxy-D-glucose
FDG-PET	2-[^{18}F] fluoro-2-deoxy-D-glucose–positron emission tomography; or fluorine-18-labelled deoxyglucose positron emission tomography
FEES	fibreoptic endoscopic evaluation of swallowing
FEESST	fibreoptic endoscopic evaluation of swallowing with sensory testing
FESS	functional endoscopic sinus surgery
FETNIM	fluorine-18 fluoroerythronitroimidazone
FFP	fresh frozen plasma
FFT	fast Fourier transform
FGF	fibroblast growth factor
FHH	familial hypocalciuric hypercalcaemia
FISH	fluorescence *in situ* hybridization
FIV	feline immunodeficiency virus
FLAIR	fluid attenuated inversion recovery
FMISO	fluorine-18 fluoromisonidazole
fMRI	functional magnetic resonance imaging
FN	facial nerve
FNA	fine-needle aspiration
FNAB	fine-needle aspiration biopsy
FNAC	fine-needle aspiration cytology
FOAR	fronto-orbital advancement and remodelling
FOI	fibreoptic orotracheal intubation
FPANS	fluticasone propionate aqueous nasal spray
FS	folliculostellate
FSH	follicle-stimulating hormone
FT	fibrous tissue
FTA	fluorescent treponemal antibody
FTA-ABS	fluorescent treponemal antibody test
FTC	frequency threshold curve
FTP	Fitness to Practise
G	guanine
G6PD	glucose-6-phosphate deficiency
Ga-67	gallium
GABA	gamma-aminobutyric acid
GABHS	group A beta-haemolytic streptococcus
GAG	glycosaminoglycan
GALT	gut-associated lymphoid tissue
GAS	Goal Attainment Scaling
G&S	group and screen
GBI	Glasgow Benefit Inventory
GBLC	geometric broken line closure
GCS	Glasgow Coma Score
G-CSF	granulocyte-colony stimulating factor
GD	Graves' disease
GERD	gastrooesophageal reflux disease
GH	growth hormone
GHABP	Glasgow Hearing Aid Benefit Profile
GHRH	growth hormone-releasing hormone
GI	gastrointestinal
GIA	gravitoinertial acceleration
GIC	glass ionomer cement
GIST	gastrointestinal stromal tumour
GLM	ground lamella of middle turbinate, middle (frontal) portion
GMC	ganglion mother cell; or General Medical Council (UK)
GM-CSF	granulocyte-macrophage colony-stimulating factor
GN	glossopharyngeal nerve
GNE	glottal-to-noise excitation
GnRH	gonadotropin-releasing hormone
GOR	gastro-oesophageal reflux
GORD	gastro-oesophageal reflux disease
GOSH	Great Ormond Street Hospital (UK)
gp	glycoprotein
GP	general practitioner
GPN	glossopharyngeal neuralgia
GPP	gingivo-periosteoplasty
G protein	guanine nucleotide-binding regulatory protein
GRB2	growth factor receptor binding protein 2

GSH	glutathione
GSPN	greater superficial petrosal nerve
GST	glutathione S-transferase
GSW	gun shot wound
GTN	nitroglycerin
GTR	guided tissue regeneration
GVHD	graft-versus-host disease
H&E	haematoxylin and eosin
H&N	head and neck
H2	histamine receptor type 2
HA	hydroxyapatite
HAART	highly active antiretroviral therapy
HAE	hereditary angioedema
HAEM	HSV-associated erythema multiforme
HAPI	Hearing Aid Performance Inventory
HB	House–Brackmann
Hb	haemoglobin
HbA	adult haemoglobin
HBO	hyperbaric oxygen
HBOT	hyperbaric oxygen therapy
HBsAg	hepatitis B surface antigen
HC	Healthcare Commission (UK)
HCA	hydroxycarbonate apatite
HCG	human chorionic gonadotrophin
HCSU	Health Care Standards Unit (UK)
Hct	haematocrit
HCV	hepatitis C virus; or human T-lymphocytic virus 1
HD	haemodialysis
HDL	high-density lipoprotein
HDM	house dust mite
HDPE	high-density polyethylene
HDU	high dependency unit
He-Ne	helium-neon
HEp-2	human epithelial type 2
HFT	hereditary familial telangiectasia
HGF	hepatocyte growth factor
HHI	Hearing Handicap Inventory
HHIE	Hearing Handicap Inventory for the Elderly
HHT	hereditary haemorrhagic telangiectasia
HHV-6	human herpesvirus 6
HHV-8	human herpesvirus 8
HI	hearing impaired
HiB	*Haemophilus influenzae* B
HIT	heparin-induced thrombocytopenia
HITT	heparin-induced thrombocytopenia with thrombosis
HIV	human immunodeficiency virus
HIV-SGD	HIV-associated salivary gland disease
HJB	high jugular bulb
HL	hearing loss; or hearing level; or hairy leukoplakia
HLA	human leukocyte antigen
HM	history of migraine; or hemifacial microsomia
HMW	high molecular weight
HMWC	high molecular weight compound
HNC	head and neck cancer
HNR	harmonics-to-noise ratio
HNRQ	Head and Neck Radiotherapy Questionnaire
HNSCC	head and neck squamous cell carcinoma
HPA	hypothalamic–pituitary–adrenal
HPC	haemangiopericytoma
HPD	haematoporphyrin derivative
HPL	horizontal partial laryngectomy
HPT	hyperparathyroidism
HPV	human papillomavirus; or human herpes virus 8
HRA	Human Rights Act
HRCT	high-resolution computed tomography
HRM	high-resolution manometry
HRQOL	health-related quality of life
HRT	hormone replacement therapy
HS	hiatus semilunaris
h-SCC	horizontal semicircular canal
HSCT	haemopoietic stem cell transplant
HSMN	hereditary sensory-motor neuropathy
HSPG	heparin sulphate proteoglycan
HSV	herpes simplex virus
HSV-1	herpes simplex virus type 1
HSV-2	herpes simplex virus type 2
HSV-TK	herpes simplex thymidine kinase
HT	hydroxytryptamine
hTERT	human telomerase reverse transcriptase
hTR	human telomerase RNA
HU	Hounsfield unit
HUI	Health Utilities Index
HUS	haemolytic uraemic syndrome
Hz	hertz
HZV	herpes zoster virus
IAC	internal auditory canal
IAM	internal auditory meatus
IBP	invasive monitoring of blood pressure
IC	inferior colliculus; or immunochemistry
ICA	internal carotid artery
ICAM	intercellular adhesion molecule
ICAM-1	intercellular adhesion molecule 1
ICD	International Classification of Disease
ICM	intensive care medicine
ICP	intracranial pressure
ICRA	International Collegium of Rehabilitative Audiology
ICU	intensive care unit
ID	inferior dental
IDA	iron deficiency anaemia
IDT	infant distraction test
IDU	intravenous drug user
IF	intrinsic factor
IFN	interferon
IFN-α	interferon-alpha
IFN-β	inteferon-beta
IFN-γ	interferon gamma

IFNP	idiopathic facial nerve paralysis
Ig	immunoglobulin
IgE	immunoglobulin E
IGF	insulin-like growth factor
IGFI	insulin-like growth factor I
IGFII	insulin-like growth factor II
IgG	immunoglobulin G
IGS	image-guided surgery
IHAFF	International Hearing Aid Fitting Forum
IHC	immunohistochemistry; or inner hair cell
IHS	International Headache Society
IL	interleukin
IL-1	interleukin-1
IL-2	interleukin-2
IL-3	interleukin-3
IL-6	interleukin-6
ILMA	intubating laryngeal mask airway
IMA	internal maxillary artery
IMAL	internal maxillary artery ligation
IMF	intermaxillary fixation
IMRT	intensity-modulated radiation therapy
IMSPAC	imitative test of speech pattern contrast perception
INC	immunonuclear chemistry
INE	intranasal ethmoidectomy
INO	internuclear ophthalmoplegia
iNOS	inducible nitric oxide synthase
INR	international normalized ratio; or interventional neuroradiology
IOC	Interim Orders Committee (UK)
IOPI	Iowa Oral Performance Instrument
IP_3	1,4,5-inositol triphosphate
IPSS	inferior petrosal sinus sampling
IRMA	immunoradiometric assay
IRS	Intergroup Rhabdomyosarcoma Study
ISAAC	International Study of Asthma and Allergies in Childhood
ISEL	*in situ* end labeling
ISJ	incudostapedial joint
ISO	International Standards Organization
ISS	immunostimulatory DNA sequence
ISSNHL	idiopathic sudden sensorineural hearing loss
IT	inferior turbinate
ITA	inferior thyroid artery
ITE	in the ear
ITP	idiopathic thrombocytopenic purpura
ITU	intensive therapy unit
IUCC	International Union against Cancer
i.v.	intravenous
IVIg	intravenous immunoglobulin
JFC	just-follow-conversation
JNA	juvenile nasopharyngeal angiofibroma
JORPP	juvenile-onset recurrent respiratory papillomatosis
K	Kirschner
KAR	killer activating receptor
keV	kilo electron volt
KIR	killer inhibitory receptor
KS	Kaposi's sarcoma
KSS	Kearns–Sayre syndrome
KTP	potassium titanyl phosphate
LA	lymphangioma
LAD	leukocyte adhesion defect
LAP	left anteroposterior
LARP	left anterior–right posterior
LAUP	laser-assisted uvulopalatoplasty
LB	lateral bundle
LCH	Langerhans' cell histiocytosis
LCM	laser capture microdissection
LD	lymphocytic depleted
LDH	lactate dehydrogenase
LDL	low-density lipoprotein; or loudness discomfort level
LDUH	low-dose unfractionated heparin
LED	light-emitting diode
LFA	lymphocyte-function associated antigen
LGOB	loudness growth in octave bands
LH	luteinizing hormone
LHRH	leuteinizing hormone-releasing hormone
LIF	leukaemia-inhibitory factor
LINks	Local Involvement Networks (UK)
LL	lateral lemniscus
LM	laryngeal mask
LMA	laryngeal mask airway
LMN	lower motor neuron
LMW	low molecular weight
LMWC	low molecular weight compound
LMWH	low molecular weight heparin
LOD	logarithm to the base 10 of the odds that the markers are linked at a recombination distance of N centimorgans
LOH	loss of heterozygosity
LOS	length of stay; or lower oesophageal sphincter
LP	lamina papyracea; or lichen planus; or lymphocyte predominant
LPC	linear predictive coding
LPR	laryngopharyngeal reflux
LR	likelihood ratio
LREC	local research ethics committee
LSCC	lateral semicircular canal
LT	leukotriene
LTAS	long-term average spectrum
LTASS	long-term average speech spectrum
LTB	laryngotracheobronchitis; or laryngotracheobronchoscopy
LTC4-S	leukotriene C4 synthase
LTR	laryngotracheal reconstruction
LTRA	leukotriene receptor antagonists
LVA	large vestibular aqueduct

LVAS	large vestibular aqueduct syndrome
LVN	lateral vestibular nuclei
LVOR	linear vestibulo–ocular reflex
M	metastases
MAb	monoclonal antibodies
MABP	mean arterial blood pressure
MAC	membrane attack complex; or *Mycobacterium avium* complex
MACS	magnetic-activated cell sorter; or minimal access cranial suspension
MAF	minimum audible field
MALT	mucosa-associated lymphoid tissue
MAOI	monoamine oxidase inhibitor
MAP	minimum audible pressure
MAPK	mitogen-activated protein kinase
MAS	mandibular advancement splint
MB	medial bundle
MBL	mannose-binding lectin
MBP	major basic protein
MBS	modified barium swallow
MCP	monocyte chemotactic protein
MCP-1	monocyte chemotactic protein-1
MCS	mental component summary
M-CSF	macrophage-colony stimulating factor
MCV	mean corpuscular volume
MDC	macrophage derived chemokine
MDR	multiple drug resistance
MDRTB	multidrug resistant tuberculosis
MDS	myelodysplastic syndrome
MDT	multidisciplinary team
MDVP	Multidimensional Voice Program
ME	middle ear
MEE	medial edge epithelium
MEG	magnetoencephalography
MEK	MAPK/extracellular signal related kinase
MELAS	mitochondrial encephalopathy, lactic acidosis and stroke-like episode
MEMS	microelectromechanical system
MEN	multiple endocrine neoplasia
MERRF	myoclonic epilepsy and ragged red fibre
MeSH	medical subject heading
MESS	microscopic endonasal sinus surgery
MET	middle ear transducer
MF	middle fossa
M-FISH	multifluor FISH
MFR	mean airflow rate
MGB	medial geniculate body
MGSA	melanoma growth stimulating activity
MGUS	monoclonal gammopathy of uncertain significance
MHC	major histocompatibility complex
MI	myocardial infarction
MIBG	metaiodobenzylguanidine; or iodine-123-metaiodobenzylguanidine
MIBI	sestamibi; or technetium-99m
MIC	minimum inhibitory concentration
MIDD	maternally inherited diabetes and deafness
MIP	minimally invasive open parathyroidectomy; or maximum intensity projection; or macrophage inflammatory protein
MIP-1α	macrophage inflammatory protein-1α
MISS	minimally invasive sinus surgery
MIT	monoiodotyrosine
MIVAP	minimally invasive video-assisted parathoidectomy
ML	mixed cellularity
MLD	masking level difference
MLF	medial longitudinal fascicle or fasciculus
MLR	middle latency response
MLTB	microlaryngotracheobronchoscopy
MM	malignant melanoma
MMC	mitomycin C
MMN	mismatch negativity
MMP	mucous membrane pemphigoid; or matrix-metalloprotease
MMR	measles, mumps and rubella
MMS	Moh's micrographic surgery
MND	motor neurone disease
MNG	multinodular goitre
MOC	medial olivocochlear
MODS	multiple organ dysfunction syndrome
MOT	malignant odontogenic tumour
MPA	microscopic polyangiitis
MPL	monophosphoryl lipid A
MPO	myeloperoxidase
MPT	maximum phonation time
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MR	magnetic resonance
MRA	magnetic resonance angiography
MRC	Medical Research Council (UK)
MREC	multicentre regional ethics committee
MRI	magnetic resonance imaging
MRL	minimal response level
mRNA	messenger ribonucleic acid
MRND	modified radical neck dissection
MRS	Melkersson–Rosenthal syndrome; or magnetic resonance sialography
MRSA	methicillin-resistant *Staphylococcus aureus*
MRV	migraine-related vestibulopathy
MS	multiple sclerosis
MSA	multiple systems atrophy
MSBOS	maximum surgical blood ordering schedule
MSG	monosodium glutamate
MST	maximal stimulation test
MT	maxilloturbinal; or middle turbinate
MTC	medullary thyroid carcinoma
MTD	muscle tension dysphonia
mtDNA	mitochondrial DNA
MTHFR	methylenetetrahydrofolate reductase
mTHPC	meso-tetra (hydroxyphenyl) chlorin
MUS	medically unexplained symptom

MV	mechanical ventilation
MVN	medial vestibular nuclei
N	nodal
NA	noradrenaline
NADP	nicotinamide adenine dinucleotide phosphate
NADPH	reduced form of nicotinamide adenine dinucleotide phosphate
NAL	National Acoustic Laboratories (Australia)
NAMCS	National Ambulatory Medical Care Survey (USA)
NANIPER	nonallergic noninfectious perennial rhinitis
NARES	nonallergic rhinitis with eosinophilia syndrome
NATA	National Anonymous Tonsil Archive
NBCA	n-butyl-2-cyanoacrylate; or N-butyl-cyanoacrylate
NBT	nitro blue tetrazolium
NCAA	National Clinical Assessment Authority (UK)
NCAS	National Clinical Assessment Service (UK)
NCASP	National Clinical Audit Support Programme (UK)
NCCG	non-consultant career-grade
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Data Base (USA)
NCEPOD	National Confidential Enquiry into Patient Outcome Death (UK)
NCIC	National Cancer Institute of Canada
NEET	nose, ear, eye and temple
NESSTAC	North of England and Scotland Study on Tonsillectomy and Adenoidectomy in Children
NET	nerve excitability test
NFκB	nuclear factor kappa B
NF1	neurofibromatosis type 1
NF2	neurofibromatosis type 2
NFA	nonfunctioning pituitary adenomas; or nasofrontal approach
NG	nasogastric
NH	normal hearing
NHL	non-Hodgkin's lymphoma
NHS	National Health Service (UK)
NHSP	Newborn Hearing Screening Programme
NIBP	automatic noninvasive blood pressure
NICE	National Institute for Health and Clinical Excellence (UK)
NICU	nonimmunological contact urticaria; or neonatal intensive care unit
NIDDM	noninsulin dependent diabetes mellitus
NIH	National Institutes of Health (USA)
NIHL	noise-induced hearing loss
NIPF	nasal inspiratory peak flow
NIS	Na+/I– symporter
NK	natural killer
N/m^2	Newtons/square metre
NMCC	nasal mucociliary clearance
NMDA	N-methyl-d-aspartate; or National Minimum Data Set (UK)
NNE	normalized noise energy
NNT	number needed to treat
NO	nitric oxide
NO_2	nitric dioxide
NOE	naso-orbito-ethmoid
non-REM	nonrapid eye movement sleep
NOS	not otherwise specified
NP	nasopharynx; or nasopharyngeal
NPC	nasopharyngeal cancer; or nasopharyngeal carcinoma
NPSA	National Patient Safety Agency (UK)
NPTA	National Prospective Tonsillectomy Audit (UK)
NPV	negative predictive value
NPY	neuropeptide Y
NRA	nucleus retroambigualis
NRLS	National Reporting and Learning System (UK)
NRT	neural response telemetry
NS	nodular sclerosing
NSAID	nonsteroidal antiinflammatory drug
NSCAG	National Specialist Commissioning Advisory Group (UK)
NSF	national service framework
NSHPT	neonatal severe hyperparathyroidism
NSRAN	nonsyndromic recessive auditory neuropathy
NT	nasoturbinal
NTD	neural tube defect
NTM	non-tuberculous mycobacteria
NTS	nucleus tractus solitarius
NYHA	New York Heart Association
O_3	ozone
OAE	otoacoustic emission
OAN	olfactory neuroblastoma
OAS	oral allergy syndrome
OB	olfactory bulb
OCB	olivocochlear bundle
OCFC	open controlled food challenge
OCT	optical coherence tomography
ODI	oxygen desaturation index
ODT	olfactory detection threshold
OEC	olfactory ensheathing cell
OFG	orofacial granulomatosis
OGTT	oral glucose tolerance test
OHC	outer hair cell
OHL	oral hairy leukoplakia
OHS	obesity hypoventilation syndrome
OKN	optokinetic nystagmus
OM	occipitomental
OMC	ostiomeatal complex
OME	otitis media with effusion
OMENS	orbit, mandible, ears, nerves and soft-tissue

OMIM	Online Mendelian Inheritance in Man
OPCS	Office for Population Censuses and Surveys (UK)
OPG	orthopantomogram
OR	occupational rhinitis
OREP	olfactory event-related potential
ORL	otorhinolaryngology
OS	osteosarcoma
OSA	obstructive sleep apnoea
OSAH	obstructive sleep apnoea/hypopnoea
OSAHS	obstructive sleep apnoea/hypopnoea syndrome
OSAS	obstructive sleep apnoea syndrome
OSC	overview and scrutiny committee
OSPH	ostium of sphenoid sinus
OSPL	output sound pressure level
OTOF	otoferlin
OVAR	off-vertical axis rotation
P	phosphate; or posterior
PA	pernicious anaemia
PAC	P1 artificial chromosome; or pulmonary artery catheter
PAD	preoperative autologous deposit
PAF	platelet-activating factor
PAG	periaqueductal grey matter
PAI-1	plasminogen activator inhibitor type 1
PALS	Patient Advice and Liaison Service (UK)
PA-RT	partly accelerated radiotherapy
PAS	periodic acid–Schiff
PBP	progressive bulbar palsy
PCA	patient-controlled analgesia
PCC	prothrombin complex concentrate; or Professional Conduct Committee (UK)
PCD	primary ciliary dyskinesia
PCHI	permanent childhood hearing impairment
PCNA	proliferating cell nuclear antigen
PCR	polymerase chain reaction
Pcrit	critical pressure
PCS	physical component summary
PCT	primary care trust
PCTR	partial cricotracheal resection
PD	Parkinson's disease
PD-ECGF	platelet-derived endothelial cell growth factor
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PDL	pulsed dye laser
PDR	*Physicians' Desk Reference*
PDS	polydimethylsiloxane
PDT	photodynamic therapy
PE	polyethylene; or pulmonary embolism; or pharyngo–oesophageal
PEEP	positive-end expiratory pressure
PEG	percutaneous endoscopic gastrostomy
PEMA/THFMA	poly (ethylmethacrylate)/tetrahydrofurfuryl methacrylate
PET	polyethylene terephthalate; or positron emission tomography
PET-CT	positron emission tomography/computed tomography
PF	posterior fontanelle; or cisplatinum/5-fluorouracil
PF4	platelet factor 4
PFAPA	periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis
PFC	perfluorocarbon
PFG	percutaneous fluoroscopic gastrostomy
PGA	polyglycolic acid
PGE_1	prostaglandin-E_1
PGI_2	prostacycline; or prostaglandin I_2
PGL	persistent generalized lymphadenopathy
pHPT	primary hyperparathyroidism
PI	pulsatility index
PI3-K	phosphotidyinositol 3
PICA	posterior inferior cerebellar artery
PICU	paediatric intensive care unit
PIF	prolactin release inhibiting factor
PIFR	peak inspiratory flow
PIHA	partially implantable hearing aid
PIII	parathyroid III
PIV	parainfluenza virus; or parathyroid IV
PIVC	parietoinsular vestibular cortex
PLA	polylactic acid
PLD	potentially lethal damage
PLF	congenital perilymphatic fistula
PLG	polylactide-coglycolide
PLMD	periodic limb movement disorder
PLS	primary lateral sclerosis
PM	particulate matter
PMS	pharyngeal mucosal space
PNP	purine nucleoside phosphorylase; or paraneoplastic pemphigus
PNS	peripheral nervous system; or postnasal space
POGO	prescription of gain and output
PONV	postoperative nausea/vomiting
PORP	partial ossicular replacement prosthesis
PP	pyrophosphate
PPC	Preliminary Proceedings Committee (UK)
PPD	purified protein derivative
PPI	proton pump inhibitor; or patient and public involvement
PPRF	parapontine reticular formation; or paramedian pontine reticular formation
PPS	parapharyngeal space
PPV	positive predictive value
PR3	proteinase 3
PRCT	prospective randomized controlled trial
PRL	prolactin
PRP	platelet-rich plasma
PRPP	5-phospho-alpha-D-ribose 1-diphosphate
PRS	persistent rhinosinusitis
PRV	polycythaemia rubra vera

PSA	prostate-specific antigen; or pleomorphic salivary adenoma; or persistent stapedial artery
p-SCC	posterior semicircular canal
PSG	polysomnography
PS-OCT	polarization-sensitive OCT
PSP	progressive supranuclear palsy
PSV	peak systolic velocity
PT	prothrombin time
PTA	pure tone average; or peritonsillar abscess
PTC	psychophysical tuning curve
PTFE	polytetrafluoroethylene
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related protein; or parathyroid hormone-related peptide
pTNM	pathological tumour, nodes, metastases
PTP	post-transfusion purpura
PTS	permanent threshold shift
PTU	propylthiouracil
PU	uncinate process
PV	pemphigus vulgaris
PVA	polyvinyl alcohol
PVC	polyvinyl chloride
PVCN	posteroventral cochlear nuclei
PVP	pause vestibular position; or position vestibular pause
PVS	persistent vegetative state
PZT	lead zirconate titanate
QALY	quality adjusted life year
QOL	quality of life
QTL	quantitative trait loci
RA	retinoic acid
RAE	Ring, Adair, Elwyn
RAI	radioactive iodine
RALP	right anterior–left posterior
RAM	Rahmonic amplitude
RANTES	regulated on activation, normal T-cell expressed and secreted
RAP	right anteroposterior
RARα	retinoic acid receptor α gene
RARS	recurrent acute rhinosinusitis
RAS	recurrent aphthous stomatitis
RAST	radioallergosorbent test
RAT	rapid antigen testing
RB	retinoblastoma
RBC	red blood cell
rCBF	regional cerebral blood flow
RCPCH	Royal College of Paediatrics and Child Health
RCT	randomized controlled trial
RDI	respiratory disturbance index
REAG	real-ear aided gain
REAL	Revised European American Lymphoma
RECD	real ear to coupler difference
REIG	real-ear insertion gain
REM	rapid eye movement
rEPO	recombinant erythropoietin
RET	rearranged during transfection
RFS	rhinofrontal sinuseptotomy
RFTVR	radiofrequency tissue volume reduction
RFVR	radiofrequency volumetric reduction
RHD	Reported Hearing Disability
RI	resistance index
RIA	radioimmuno assay
riMLF	rostral interstitial nucleus of the medial longitudinal faciculus
RLN	recurrent laryngeal nerve
RLS	restless leg syndrome
RMS	root mean square; or rhabdomyosarcoma
RNA	ribonucleic acid
RND	radical neck dissection
RNID	Royal National Institute for Deaf and Hard of Hearing People (UK)
RNP	ribonucleoprotein
ROC	receiver operating characteristic
ROI	region of interest; or reactive oxygen intermediate
ROM	range of motion
ROOF	retro-orbicularis orbital fat
ROS	reactive oxygen species
RP	rapid prototyping
RPA	retropharyngeal abscess
RPT	rapid pull through
RR	relative risk
RRP	recurrent respiratory papillomatosis
RRR	relative risk reduction
RS	retrosigmoid
RSDI	Rhinosinusitis Disability Index
RSOM	rhinosinusitis outcome measure
RSTL	relaxed skin tension line
RSV	respiratory syncytial virus
RT	radiotherapy
rT3	reverse triiodothyronine
RTK	receptor tyrosine kinase
RTL	right thyroid artery
rTMS	repetitive low-frequency transcranial magnetic stimulation
RT-PCR	reverse transcriptase-polymerase chain reaction
RUDS	reactive upper airways dysfunction syndrome
SACE	serum angiotensin converting enzyme
SAD	supraglottic airway device
SAGM	saline-adenine-glucose-mannitol
SALT	speech and language therapist
SANS	subacute necrotizing sialadenitis
SAP	signalling lymphocyte activation molecule associated protein
SAPALDIA	Swiss Study on Air Pollution and Lung Diseases in Adults
SBS	sick building syndrome

s.c.	subcutaneous
SCBU	special care baby unit
SCC	squamous cell carcinoma or cancer; or semicircular canal
SCCA	squamous cell carcinoma antigen
SCCHN	squamous cell carcinoma of the head and neck
SCD	sickle cell disease
SCF	stem cell factor
SCID	severe combined immunodeficiency
SCN	severe congenital neutropenia
SCUBA	self-contained underwater breathing apparatus
$ScvO_2$	central venous oxygen saturation
SEAC	Spongiform Encephalopathy Advisory Committee
SEM	scanning electron microscopy
sEMG	surface electromyography
SF-36	Medical Outcome Study Short-Form 36-Item Health Survey
SfBH	Standards for Better Health (UK)
SFF	speaking fundamental frequency
SFOAE	stimulus frequency otoacoustic emission
SGC	spiral ganglion cell
Shh	sonic hedgehog
SHO	senior house officer
SHOT	serious hazards of transfusion
SIADH	syndrome of inappropriate antidiuretic hormone
SIDS	sudden infant death syndrome
sIg	surface immunoglobulin
SIGN	Scottish Intercollegiate Guidelines Network
SIMEHD	semi-implantable middle ear electromagnetic hearing device
SIP	sickness impact profile
SIR	speech intelligibility rating; or standardized incidence ratio
SIRS	systemic inflammatory response syndrome
SL	sensation level
SLD	sublethal damage
SLE	systemic lupus erythematosus
SLIT	sublingual immunotherapy
SLN	superior laryngeal nerve
SLNB	sentinel lymph node biopsy
SLP	superficial lamina propria
SLT	speech and language therapist
SMAS	superficial or subcutaneous muscloaponeurotic system
SMOFIT	submucous resection of the turbinate
SMR	submucosal resection
SMS	short message service; or indium-111 pentetreotide
S/N	speech-to-noise
SNC	sinonasal cancer
SNHL	sensorineural hearing loss
SNOMED	Systematized nomenclature of medicine
SNOMED CT	Systematized Nomenclature of Medicine – Clinical Terms
SNOT	sino-nasal outcome test
SNR	signal-to-noise ratio
SNUC	sinonasal undifferentiated carcinoma
SO_2	sulphur dioxide
SOAE	spontaneous otoacoustic emission
SOC	superior olivary complex
SOM	secretory otitis media
SOOF	suborbicularis oculi fat
SOS	guanine nucleotide exchange factor (son of sevenless)
SP	substance P; or summating potential
SPECT	single photon emission computed tomography
SPET	single photon emission tomography
SPF	sphenopalatine foramen
SPI	soft phonation index
SPIO	superparamagnetic iron oxide
SPL	sound pressure level
SPT	skin prick test; or station pull through
SRS	subacute rhinosinusitis
SRS-A	slow reacting substance of anaphylaxis
SRT	speech recognition threshold; or speech reception threshold
SSC	superior semicircular canal
SSEP	steady-state potential
SSG	split skin graft
SSLP	simple sequence length polymorphism
SSNHL	sudden sensorineural hearing loss
SSPE	subacute sclerosing panencephalitis
SSPL	saturation sound pressure level
SSR	steady-state response
SSRI	selective serotonin reuptake inhibitor
ST	superior turbinate
STAT	signal transducer and activator of transcription
STD	standard deviation
STIR	short time inversion recovery
STRP	short tandem repeat polymorphism
SUV	standardized uptake value
SVCO	superior vena caval obstruction
SVL	strobovideolaryngoscopy
SVN	superior vestibular nuclei; or superior vestibular nerve
SVV	subjective visual vertical
SVZ	subventricular zone
SWS	slow wave sleep
T	thymine; or tumour
T1WI	T1-weighted images
T2WI	T2-weighted images
T3	triiodothyronine
T4	thyroxine
T/A	tonsillectomy and/or adenoidectomy
TAGVHD	transfusion-associated graft-versus-host disease

TARC	thymus and activation-regulated chemokine
TARGET	Trial of Alternative Regimens in Glue Ear Treatment
TB	tuberculosis; or *Mycobacterium tuberculosis*
TBG	thyroxine-binding globulin
Tc	T cytotoxic
Tc-99m	technetium
Tc-99m (v) DMSA	pentavalent dimercaptosuccinic acid
TC	thyroid cartilage
TCF	tracheocutaneous fistula
TCI	target-controlled infusion
TCP	tricalcium phosphate
TCR	T cell receptor
TdT	terminal deoxynucletidyl transferase
TEC	Tissue Engineering and Regenerative Medicine Centre
TENS	transcutaneous electrical nerve stimulation
TEOAE	transient evoked otoacoustic emission
TEP	tracheo-oesophageal puncture
TFG	temporalis fascia graft
TFT	thyroid function test
TG	thyroglobulin
TGF	transforming growth factor
TGF-α	transforming growth factor alpha
TGF-β	transforming growth factor beta
TGF-β1	transforming growth factor beta 1
Th	T helper
TIA	transient ischaemic attack
TIBC	total iron binding capacity
TICA	totally implantable cochlear amplifier
TKI	tyrosine kinase inhibitor
TM	tympanic membrane
TMC1	transmembrane channel-like gene 1
TMD	temporomandibular disorder
TMJ	temporomandibular joint
TMTF	temporal modulation transfer function
TN	trigeminal neuralgia; or trigeminal nerve
TNF	tumour necrosis factor
TNF-α	tumour necrosis factor alpha
TNM	tumour, node, metastasis
TOAE	transient evoked otoacoustic emission
TOE	transoesophageal echocardiography; or *Trichophyton*, *Oidiomycetes* and *Epidermophyton*
TOF	tracheo-oesophageal fistula
TOF-o-gram	tracheo-oesophageal fistulogram
TORP	total ossicular replacement prosthesis
TPA	tissue polypeptide antigen
TPF	docetaxel/cisplatinum/5-fluorouracil; or temporoparietal fascia
TPHA	*T. pallidum* haemagglutination test; or treponemal haemagglutination
TPI	*T. pallidum* immobilization
TPN	total parenteral nutrition
TPO	thyroid peroxidase; or thyroperoxidase
Tpot	potential doubling times
TQM	total quality management
TRALI	transfusion-related acute lung injury
TRAM	transverse rectus abdominis myocutaneous
TRH	thyrotropin-releasing hormone
tRNA	transfer ribonucleic acid
TRP	transient receptor potential
TRT	tinnitus retraining therapy
TSG	tumour suppressor gene
TSH	thyroid-stimulating hormone; or thyrotropin
TSHoma	TSH-secreting adenoma
TSS	transitional space surgery
TT	thrombin time
TTN	thalamic taste nucleus
TTP	thrombotic thrombocytopeniac purpura
TTR	transthyretin
TTS	temporary threshold shift
TUNEL	TdT-mediated nick end labelling
TXA_2	thromboxane A_2
U	uracil
UADT	upper aerodigestive tract
UARS	upper airway resistance syndrome
UCL	uncomfortable loudness level
UICC	International Union Against Cancer
UK-CCSG	United Kingdom Children with Cancer Study Group
UKCISG	UK Cochlear Implant Study Group
UMN	upper motor neuron
UMP	uridine monophosphate
UNICEF	United Nations Children's Fund
UOS	upper oesophageal sphincter
UP	uncinate process
UPP	uvulopalatopharyngoplasty
UPPP	uvulopalatopharyngoplasty
UPSIT	University of Pennsylvania Smell Identification Test
URT	upper respiratory tract
URTI	upper respiratory tract infection
US	ultrasound; or ultrasonography
USH	Usher syndrome
USH1B	Usher syndrome type 1B
USPIO	ultra-small super paramagnetic iron oxide
UV	ultraviolet
uVD	unilateral vestibular deafferentiation
UVPP	uvulopalatopharyngoplasty
UWQOL	University of Washington Quality of Life Questionnaire
VA	Veterans' Affairs; or vestibular aqueduct
VAAP	voice activity and participation
VAC	vacuum-assisted closure
VAM	variation of amplitude
VAS	visual analogue scale; or visual analogue score
VATER	vertebral, anal, tracheooesophageal and radial
VCA	viral capsid antigen

VCAM-1	vascular cell adhesion molecule-1
vCJD	variant Creutzfeldt-Jakob disease
VCR	vestibulocollic reflex
VDRL	Venereal Disease Research Laboratory
VEES	video endoscopic evaluation of swallowing
VEGF	vascular endothelial growth factor
VEMP	vestibular-evoked myogenic potential
VEP	vestibular evoked potential
VFSS	videofluoroscopic swallowing study
VHI	Voice Handicap Index
VHI-10	Voice Handicap Index-10
VHL	Von Hippel–Lindau
VHQ	Vertigo Handicap Questionnaire
VHT	vestibular habituation training
VILI	ventilator induced lung injury
VIP	vasoactive intestinal polypeptide
VLA	very late activation antigen
VLA4	very late activation antigen 4
VLDL	very low-density lipoprotein
VMA	vanillylmandelic acid
VN	vestibular nuclei; or vagus nerve
VOC	volatile organic compound
VOG	video-oculography
VoiSS	voice symptom scale
VOR	vestibulo-ocular reflex
VORP	vibrating ossicular prosthesis
VORS	vestibulo-ocular reflex suppression
VPI	velopharyngeal insufficiency
VPQ	patient questionnaire of vocal performance
VRA	visual reinforcement audiometry
VRE	vancomycin-resistant enterococci
V-RQOL	voice-related quality of life
VS	vestibular schwannoma
VSM	velocity storage mechanism
VSR	vestibulospinal reflex
VTE	venous thromboembolism
VVI	vocal velocity index
vWD	von Willebrand disease
vWF	von Willebrand factor
VZV	varicella zoster virus
WAS	Wiskott Aldrich syndrome
WBC	white blood cell
WHO	World Health Organization
WMD	weighted mean difference
WOB	work of breathing
WP	Woodruff's plexus
WPC	WARN, PAUSE, CHECK
XHIM	X-linked hyper immunoglobin M
XLA	X-linked agammaglobulinaemia
XLP	X-linked lymphoproliferative syndrome
YAC	yeast artificial chromosome
YAG	yttrium aluminium garnate

PART 1

CELL BIOLOGY

EDITED BY NICHOLAS S JONES

1

Molecular biology

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SEARCH STRATEGY

The data in this chapter are supported by a Medline search using the key words molecular biology, genetics, and cell biology.

INTRODUCTION

Molecular biology describes the study of the biochemical processes that govern the behaviour of cells. These processes form the fundamental mechanisms by which cell function, cell–cell interactions and cell turnover are regulated. Disruption of this regulation may lead to disease, whilst an understanding of these mechanisms allows the physician to attempt to predict disease behaviour and to explore methods of restoring this regulation at a molecular level. This chapter reviews the principles of molecular genetics and outlines aspects of the molecular biology of the cell in the context of otolaryngological disease processes and describes some of the techniques that form the backbone of current molecular biology. It should give the reader sufficient background knowledge of molecular biology to understand subsequent chapters discussing the molecular biology of specific otolaryngological conditions.

MOLECULAR GENETICS: DNA STRUCTURE AND FUNCTION

Hereditary information in eukaryotes is stored in the form of double-stranded deoxyribonucleic acid (DNA) and is referred to as the genome. DNA forms a double-helix structure as a result of hydrogen bonds between complementary pairs of nucleotides, adenine (A) with thymine (T) and cytosine (C) with guanine (G). The nucleotides on each strand are organized linearly in triplets, known as codons. Each specific sequence determines a single specific amino acid, for example ACU specifies threonine. However, as there are more triplet combinations (64) than commonly encountered amino acids (20), some proteins may be represented by different codons (e.g. lysine by AAA as well as AAG) and some codons (UAA, UGA and UAG) are 'stop' codons, constituting a signal for arrest of translation. The overwhelming majority of this DNA (99.9 percent) exists in the cell nucleus as the nuclear genome, which, in the human, is estimated to be 3000 megabase pairs in physical size and encodes 30,000–35,000 genes. The remaining DNA (16.6 kilobase pairs) forms the mitochondrial genome, encoding 37 genes. The mitochondrial genome and its potential role in cancer diagnostics will be discussed later.

Each DNA molecule is packaged into a chromosome by complex folding of the DNA around proteins. Diploid human cells contain 22 pairs of autosomes (1 to 22) and a

pair of sex chromosomes (XX or XY) which determines the sex of the organism. One of each pair of chromosomes is maternally inherited and the other is paternally inherited. Each chromosome has a distinctive shape, size and banding pattern, but have the common appearance of two arms apparently separated by a constriction. The centromere is microscopically recognizable as the central constriction separating the chromosome into a long arm (q for queue) and a short arm (p for petit), but its biological role lies in anchoring the chromosome to the mitotic spindle for segregation during cell division. The ends of the chromosomes are capped by telomeres, which are specialized structures containing unique simple repetitive sequences. They maintain the structural integrity of the chromosome and provide a solution for complete replication of the extreme ends of the chromosome. The conventional nomenclature for chromosomal locus assignment is given by the chromosome number, followed by the arm and finally the position on the arm, for example, 3p21 indicates position 21(two-one) on the short arm of chromosome three.

During normal cell division, DNA replication is achieved by the separation of the two strands by DNA helicase. Each separated single strand then acts as a template for polymerization, catalyzed by DNA polymerase, of nucleotides forming a new complementary strand and thus double-stranded DNA identical to the original dsDNA. As each daughter DNA consists of one original and one newly synthesized DNA strand, the process is known as semi-conservative replication. The specificity of the complementary relationship between the nucleotides on each strand forms the basis for many techniques of modern molecular biology and molecular cytogenetics.[1] The accuracy with which DNA replication takes place is remarkable with an estimated error rate of less than one in 10^9 nucleotide additions. Such accuracy is of vital importance to the individual as a permanent change in DNA, or mutation may cause inactivation of a gene essential to cell survival or cell cycle control. The high fidelity of DNA sequence replication is achieved by unidirectional 5′-to-3′ direction of DNA replication, a rigorous DNA proofreading mechanism which detects mismatched DNA and efficient DNA repair pathways which excise and repair DNA damage. Failure of these mechanisms, such as is encountered in xeroderma pigmentosum, Fanconi's anaemia and ataxia telangiectasia, leads to accumulation of DNA replication errors and a high incidence of malignancies.

Although the human nuclear genome is 3×10^9 base pairs in size, about 90 percent of it is noncoding, with all the genes being coded by the remaining 10 percent of the DNA. Within the noncoding DNA are dispersed short arrays of repeat units of pairs or triplets of nucleotides (di-/trinucleotides). The exact function of these microsatellite repeats is not entirely clear, but their existence and frequency of dispersion throughout the genome have greatly facilitated study of the genetics of tumours and many inherited disorders, which will be discussed later.

A gene is a region of the chromosomal DNA that produces a functional ribonucleic acid molecule (RNA). It comprises regulatory DNA sequences which determine when and in which cell types that gene is expressed, exons which are coding sequences and interspersed introns which are noncoding DNA sequences. These regulatory sequences often consist of CpG islands, short stretches of DNA rich in dinucleotides of cytosine and guanine. The methylation status of these CpG islands determines whether that gene is expressed in a particular cell or tissue, being unmethylated in tissues where the genes are expressed. As will be discussed later, aberration of this control is one of the mechanisms of tumour suppressor gene inactivation. Transcription is the intranuclear process driven by RNA polymerase whereby one of the two DNA strands acts as a template for the synthesis of a single RNA strand which is complementary to the DNA, except that uracil replaces thymine in RNA. This primary RNA transcript then undergoes post-transcriptional processing, or splicing.[2] Traditional dogma held that one gene produces one protein and therefore splicing was considered to occur simply in order to remove the noncoding intronic sequences, producing messenger RNA (mRNA). It is now known that by 'alternative splicing', one gene can result in the production of several different but often related proteins in different tissues.[3]

The mature mRNA then migrates into the cytoplasm where it acts as a template for the synthesis of a polypeptide during translation, a process regulated and catalyzed by cytoplasmic ribosomes. Successive amino acids are added to the polypeptide chain according to the triplet code on the mRNA, which is recognized by the transfer RNA (tRNA), to which each corresponding amino acid is covalently bound. Translation is commenced upon recognition of an initiation codon (usually but not exclusively AUG/methionine) and terminated upon recognition of a stop codon. The polypeptide subsequently undergoes a variable degree of post-translational modification and/or cleavage to produce the mature protein product, which may have an intracellular role or may be exported to the endoplasmic reticulum and hence to the extracellular space to execute its function.

The mitochondrial genome is considerably smaller than the nuclear genome, but it deserves mention here because of the increasing recognition of the role of mitochondrial DNA (mtDNA) mutations in human disease. The mitochondrial genome is only 16.6 kb in size, comprising 37 genes, which encode polypeptides which are principally involved in the respiratory chain. mtDNA is double-stranded but does not form a double-helix nor does it form chromosomes, but instead it takes the form of a circular double-stranded DNA structure with a heavy and a light strand. Unlike the nuclear

genome, which is inherited from mother and father, the mitochondrial genome of an individual is entirely maternally inherited.

KEY POINTS

- The double-stranded alpha helical structure of DNA, mainly located in the nucleus, consists of nucleotide triplets called codons which code for specific amino acids and stop signals, and forms the substrate for hereditary information in eukaryotes.
- The 22 pairs of autosomes and one pair of sex chromosomes, each with their distinctive shape, size and banding pattern, represent a complex folding of DNA around proteins to give the characteristic shape of a central constriction (centromere) separating the chromosome into a long arm (q) and a short arm (p) with a telomere cap at each end to maintain structural integrity.
- Chromosome locus nomenclature: chromosome number – 3p21 – position on chromosome arm.
- Semiconservative replication of DNA during normal cell division results in the separation of two strands of DNA by DNA helicase, each strand then acting as a template for polymerization by DNA polymerase. High fidelity is vital to prevent permanent change or mutations.
- A gene is a region of chromosomal DNA which produces functional RNA consisting of:
  - regulatory DNA sequences;
  - exons, which are coding sequences;
  - introns, which are noncoding sequences.
- Transcription is the intranuclear process driven by RNA polymerase whereby one of the two DNA strands acts as a template for single-stranded RNA synthesis complementary to the DNA, except that in RNA U is replaced by T. Splicing refers to post-transcriptional processing of RNA.
- Translation is the cytoplasmic process in which mRNA acts as a template for the synthesis of polypeptide by adding successive amino acids to the polypeptide chain, according to the triplet codon of the mRNA which is recognized by the tRNA to which the corresponding amino acid is covalently bonded. This process is regulated and catalyzed by cytoplasmic ribosomes. Post-translational modification produces mature proteins.

METHODS IN MOLECULAR BIOLOGY

Basic techniques of DNA fragmentation and identification

Unlike RNA, DNA is extremely stable, which is understandable from the function that each has in the cell. For purposes of studying the DNA and in order to clone specific DNA, the DNA molecule needs to be divided into manageable fragments. Although the ability to cut (and also to join up) DNA molecules now appears to be a very straightforward process, it was only 1970 when the first restriction endonuclease was identified in a strain of *Haemophilus influenzae*, hence its name *Hin*dII (pronounced Hin-dee-two). It is believed that this restriction endonucleases act *in vivo* in bacteria as an immune or host-defence system, recognizing non-self DNA in bacteriophages and cleaving them. By surveying many different bacteria, a wide range of restriction endonucleases is now available, each of which recognize specific target sites based on sequences of four to eight nucleotides. As a specific, seven nucleotide sequence (heptanucleotide) will occur less frequently than a four nucleotide sequence (tetranucleotide), statistically, endonucleases recognizing heptanucleotide targets will cut less frequently thereby yielding larger fragments than those recognizing tetranucleotides. As the DNA is double-stranded, the resultant fragments may have blunt ends or cohesive ('sticky') ends (**Figure 1.1**). The nature of the ends of DNA fragments thus generated impact upon the way in which they can be ligated (joined) into recombinant molecules. Ligation of DNA fragments with cohesive ends is more efficient than joining of blunt-ended fragments.

ELECTROPHORESIS

Negatively charged phosphate groups on the DNA backbone confer a net negative charge on linear DNA. This allows fragments of different sizes to be resolved within a suitable gel matrix by the application of an electric current across the matrix. The DNA will migrate toward the positive electrode with the smaller fragments travelling faster than the larger fragments.[4] The size of the fragment can be estimated by the use of a graduated DNA

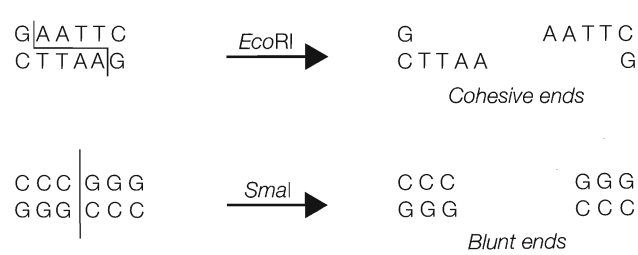


Figure 1.1 DNA cleavage by restriction endonucleases. Derived from Ref. 11, with permission.

ladder containing fragments of known molecular weight. The choice of the particular matrix depends on the fragment sizes that one is trying to resolve. Polyacrylamide gels can resolve differences of just one base pair between fragments of several hundred base pairs in size by virtue of a small pore size in the gel matrix. These gels can be used for DNA sequencing and resolution of alleles varying in only one dinucleotide repeat. Agarose gels can resolve fragment sizes from around 100 bp to 20 kb. Beyond that size, electrophoretic mobility is no longer proportional to fragment size. Resolution of fragments sizes in excess of 50 kb, such as larger bacterial artificial chromosomes (BAC) or yeast artificial chromosomes (YAC) require the use of pulsed field electrophoresis.

HYBRIDIZATION

Hybridization is the specific annealing of single DNA (or RNA) strands, the probe, to a DNA sample, the target. It serves to detect the presence of a specific sequence of DNA either in the cell or on a hybridization membrane and recognition that hybridization has occurred is achieved either by radioactively labelling the probe and localizing the radioactivity by autoradiography or by labelling the probe with fluorochromes which fluoresce when excited by light of specific wavelengths (**Figure 1.2**). Hybridization on a membrane requires the initial transfer of DNA on to a nitrocellulose membrane from an agarose gel. This elegantly simple process is eponymously known as Southern blotting after the scientist who described the process in 1975. Two other commonly used transfer techniques have their names derived from Southern blotting as jargon terms. Northern blotting is essentially the same process used for transfer of RNA to a membrane. Western blotting is one of the mainstays of protein analysis and involves the transfer of electrophoresed protein bands from a polyacrylamide gel on to a nitrocellulose or nylon membrane to which they bind strongly. Detection of the protein is usually achieved by the use of antibodies to specific antigens presented by the protein with the antibody being labelled radioactively, enzymatically or fluorescently.

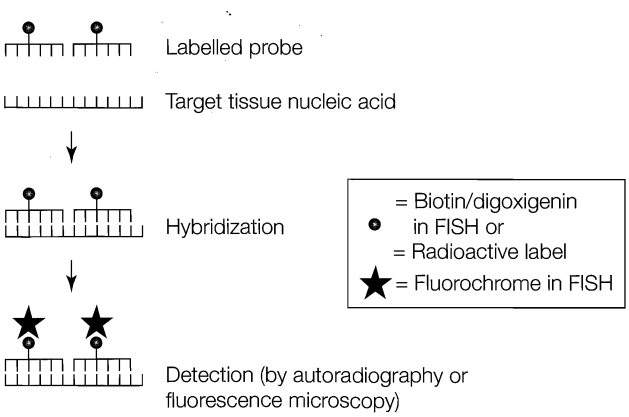


Figure 1.2 *In situ* hybridization.

CYTOGENETICS AND MOLECULAR CYTOGENETICS

Although microscopy had already reached high levels of resolution in the early 1930s, the correct number of human chromosomes was not determined until 1958. The era of classical cytogenetics was thus begun. Cytogenetics is the study of chromosomal abnormalities and rearrangements. It currently has a major role to play in prenatal diagnosis of Downs syndrome and other congenital syndromes characterized by numerical chromosomal abnormalities. In the early part of this century, Theodore Boveri proposed that cancer arose from chromosomal alterations. This hypothesis was not proven until the consistent chromosomal translocation, t(9;22), was demonstrated in chronic myeloid leukaemia. Since that time, cytogenetic analysis has been the mainstay of genetic analysis in reticuloendothelial malignancies, being responsible for the identification of consistent translocations in different leukaemias. Its use in solid tumours has been hampered by the difficulties of establishing short-term primary cultures from head and neck cancers for chromosomal analysis and the erratically acquired chromosomal changes in long-term cell lines, which may have occurred *in vitro*, influenced by culture conditions. Nevertheless, some studies have identified chromosomal areas consistently showing frequent breakpoints suggesting the location of putative tumour suppressor genes (including 3p21, 5p14, 8p11, 17p21, 18q21) and gain or amplification implying the presence of putative proto-oncogenes at other sites (including 3q, 5p, 8q, 11q13). Although the refinement of karyotyping has been radically enhanced by the introduction of 24-colour combinatorial multifluor FISH (M-FISH), the resolution and therefore utility of solid tumour karyotyping remains limited.[5]

Hybridization to target DNA in cells, using fluorescence detection, is known as fluorescence *in situ* hybridization (FISH). Fluorescence *in situ* hybridization allows the analysis of copy number of a known specific DNA sequence within intact nuclei. In reticuloendothelial malignancies and solid tumour-derived cell lines, the use of both single-copy probes and centromere alpha-satellite repeat probes on metaphase preparations has enhanced and refined classical karyotyping. Interphase FISH has been applied to solid tumour sections to assess the copy number of a known sequence in breast, prostate, bladder, brain, lung and head and neck tumours.

Fluorescence-labelled hybridization has also been combined with cytogenetics to produce the powerful technique of comparative genomic hybridization (CGH).[6] Comparative genomic hybridization permits the rapid medium resolution screening of the entire genome by comparatively hybridizing matched tumour and normal DNA from a patient, which are labelled with different fluorochromes, on to normal metaphase chromosome preparations. Under red-green dual filter fluorescence microscopy and computer-aided image analysis, areas of

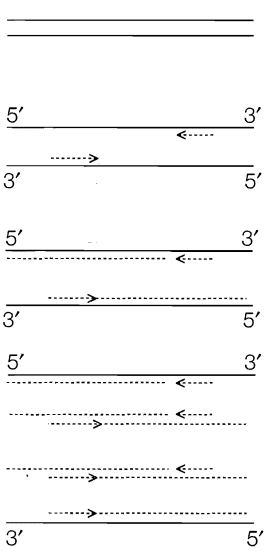
genetic 'neutrality' appear yellow, under-representation appears green, and over-representation appears red. Areas of genetic under-representation suggest the possibility of a tumour suppressor gene lying within that region while areas of over-representation may indicate the location of a putative oncogene. This technique has been applied to the rapid genetic analysis of many tumour types including squamous cell carcinomas of the head and neck. The advent of molecular cytogenetics has obviated the need for primary short-term cultures and refined the location of chromosomal aberrations in solid tumours.

POLYMERASE CHAIN REACTION

Perhaps the single molecular technique which has had the most dramatic impact on molecular biology has been the polymerase chain reaction (PCR). The original problem lay in obtaining sufficient quantities of a particular DNA sequence such that DNA profiling (e.g. sequencing) and DNA manipulation (e.g. cloning) could be achieved. The only 'requirement' is that the sequences flanking the stretch of DNA of interest is known. With that proviso, PCR achieves faithful and exponential amplification of a specific sequence of DNA by repeated cycles each consisting of dsDNA denaturation, hybridization of specific oligonucleotides (primers) and extension of the polynucleotide by rapidly altering the reaction temperature between segments of each cycle. dsDNA denaturation is achieved by raising the temperature of the reaction to 94°C for 30 seconds, thus disrupting the hydrogen bonds between the strands and exposing the hydrogen bond donor and acceptor groups to allow base pairing. The oligonucleotide primers are then allowed to hybridize to the denatured DNA (annealing) at around 55–65°C for 90 seconds before the reaction temperature is raised to 72°C to permit extension of the DNA strand by DNA polymerase in the presence of deoxynucleoside triphosphates (dNTPs). With each cycle resulting in the doubling of the copies of the DNA sequence, a 30-cycle PCR taking approximately two hours would amplify a single copy of a DNA sequence 268 million-fold (**Figure 1.3**). Although the PCR was originally described by Mullis and Faloona in 1987, one practical problem prevented its instant exploitation.[7] The DNA polymerase used in the original reaction was denatured during the DNA denaturation segment and therefore had to be added after each and every cycle. The solution came in 1989 when Lawyer isolated and characterized the DNA polymerase, Taq polymerase, from the thermophilic bacterium *Thermus aquaticus* which normally resided in temperatures above 95°C.[8] This polymerase was therefore 'heat resistant' and did not need to be replenished between cycles.

The PCR holds a central position in many molecular biological techniques as well as clinical diagnostic methods. The fundamental principle of DNA amplification has been adapted to amplify messenger RNA and to amplify areas where the initial flanking oligonucleotide sequences are not known. It is often described as a sensitive and powerful technique, but with great power comes the potential for corruption! In theory, a single copy of DNA can be amplified. Therefore, careless experimental technique may lead to contamination of the DNA sample with other DNA (e.g. from the skin of the investigator) and consequently to an artefactual result. The Taq polymerase originally described in the technique does not have proofreading properties, but newer cloned enzymes such as Pfu polymerase incorporates a proofreading function to increase amplification fidelity for sequencing reactions.

The sensitivity of PCR also presented a problem for the analysis of genetic alterations in certain solid tumours. Squamous cell carcinomas of the head and neck are histologically often characterized by a large stromal element within the tumour. The genetic alterations in the tumour may not be present in the stromal



Segment 1: Denaturation of double-stranded DNA by heating to 94°C

Segment 2: Annealing of oligonucleotide primers at 55–65°C

Segment 3: Extension of new strands by polymerase at 72°C

Cycles repeat resulting in exponential and accurate duplication of target DNA

A programme of 28 cycles generates over 67 million copies

Figure 1.3 The polymerase chain reaction.

tissue and thus total DNA extracted from the tumour will contain DNA from both benign and malignant tissue. This *in situ* contamination can now be eliminated by the use of laser capture microdissection (LCM) of tumours. LCM involves the placement of a laser-activated film over a tissue specimen. When areas of 'pure' tumour cells are identified, a focal laser pulse lifts the tissue on to the film in specimens down to 30 μm in diameter.[9]

KEY POINTS

- Restriction endonucleases are enzymes that were initially identified in bacteria that can cut and join up DNA. They recognize specific target sites based on sequences of four and eight nucleotides.
- Electrophoresis is a technique for resolving the size of DNA fragments, which carry a negative charge from the phosphate groups on their backbone. Using a gel matrix with an electric current applied across it, the DNA will migrate to the positive electrode at a rate inversely proportional to its size.
- Hybridization is the specific annealing of single DNA or RNA strands (probe) to a DNA sample (target) to detect the presence of a specific sequence of DNA in the cell or hybridization membrane. Variants include the eponomously named Southern, Northern and Western blotting techniques.
- Cytogenetics is the study of chromosomal abnormalities and rearrangements important in the diagnosis of congenital syndromes characterized by numerical chromosomal abnormalities, e.g. Downs syndrome and leukaemia types.
- FISH refers to fluorescence *in situ* hybridization which involves hybridization to target DNA cells using fluorescence detection and allows the analysis of copy number of a known specific DNA sequence within intact nuclei.
- PCR achieves faithful and exponential amplification of a specific sequence of DNA by repeated cycles each consisting of:
  - DNA denaturation by heating to 94°C to denature hydrogen bonds between strands;
  - annealing (hybridization) of oligonucleotide primers to denatured DNA at 55–65°C;
  - extension of DNA strand by DNA polymerase.

MOLECULAR ABERRATIONS OF CELLULAR BIOLOGY

Loss of heterozygosity and the expression of recessive mutant alleles

Retinoblastoma is a childhood cancer, which exhibits both hereditary and sporadic occurrence, with the inherited form transmitted as a highly penetrant autosomal dominant trait. The proposition by Alfred Knudson in 1971, based upon a statistical analysis of the occurrence of retinoblastoma in children, that two genetic events were required to inactivate the gene mitigating against development of the cancer, was a major landmark in the understanding of tumour suppressor genetics.[10] In hereditary retinoblastomas, a single additional somatic event in a cell that carried the inherited mutation was sufficient to give rise to the disease while two somatic events were required to produce a sporadic retinoblastoma. This became known as Knudson's 'two-hit' hypothesis. The subsequent study on matched tumour and blood DNA from patients with sporadic retinoblastoma by Webster Cavenee not only proved Knudson's hypothesis but also established the paradigm for all subsequent investigations of tumour suppressor genes.[11] For the first time, the now widely accepted mechanisms of tumourigenesis were reconciled, viz. that neoplasms can arise in a multistep manner, that chromosomal events can lead to tumour formation and that chromosome loss with or without reduplication can lead to expression of recessive mutations. Perhaps even more strikingly, the authors presciently suggested that development of homozygosity for recessive mutant alleles at the *Rb-1* locus may give rise to the development of other tumours and that other additional dominant mutations may be involved in the development of retinoblastoma. Cavenee proposed the various chromosomal mechanisms that could reveal recessive mutations and these are summarized for a putative tumour suppressor gene in **Figure 1.4**, adapted from the figure in his original paper. To these can now be added hypermethylation of the 5′ CpG island resulting in transcriptional inactivation of the gene, discussed below.[12] The simplest way of revealing a recessive mutant allele is by deletion of the wild-type allele, resulting in hemizygosity at the particular locus on the remaining chromosome. It is inferred from this that areas of frequent allelic loss in tumours may represent the location of putative tumour suppressor genes and this hypothesis underpins the commonly employed method of molecular detection of allelic losses, loss of heterozygosity (LOH).

The practical exploitation of the concepts outlined above hinges on the presence of the previously described microsatellites, highly polymorphic noncoding DNA sequences, also referred to as simple sequence length polymorphisms (SSLP) or short tandem repeat

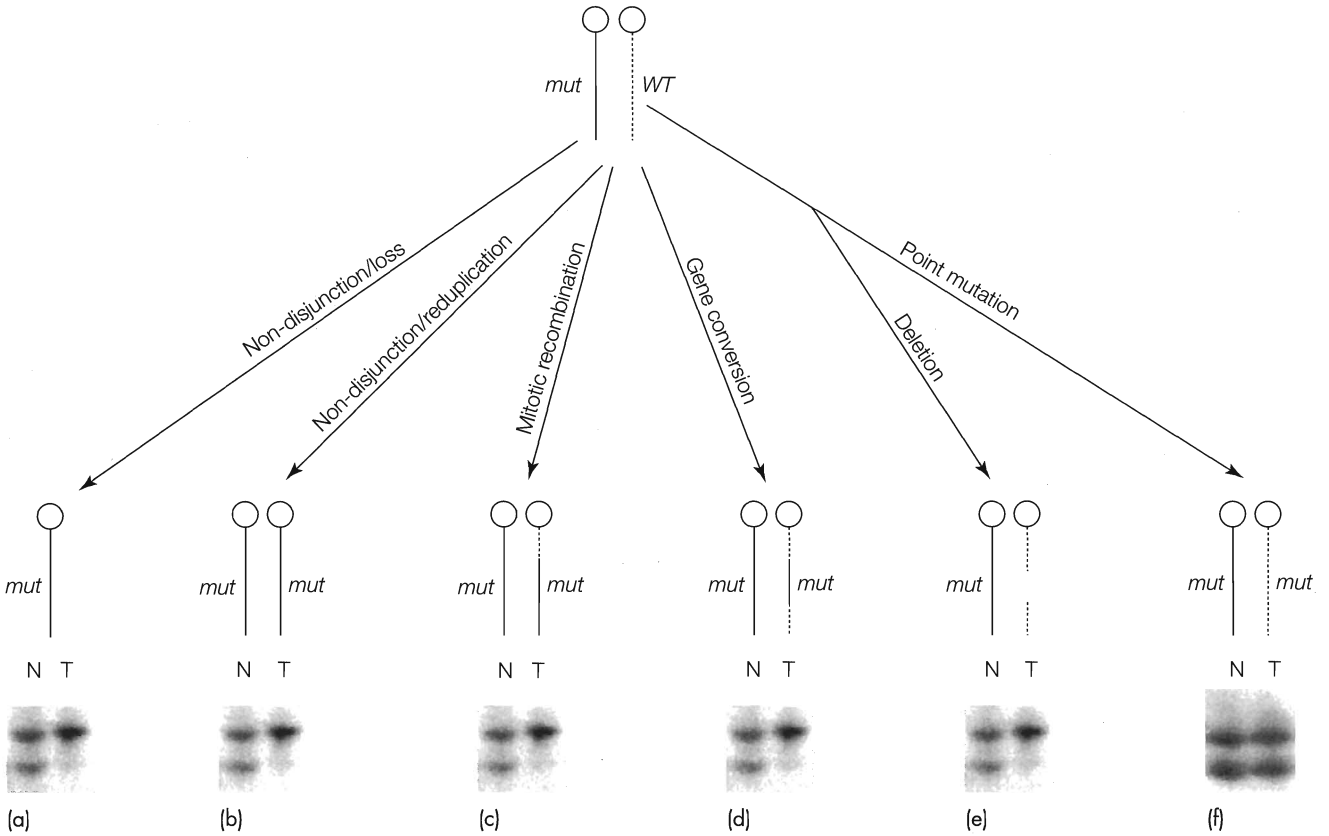


Figure 1.4 Chromosomal mechanisms that could reveal recessive mutations. In this example, before cell division, the tissue concerned carries a mutation in one copy of the hypothetical tumour suppressor gene. In each of the scenarios **(a–f)**, the recessive mutation is revealed. If the individual is heterozygous for a microsatellite marker within or very close to the mutated gene, the hypothetical PCR results are given below each ideotype. The only mechanism which escapes observed loss of heterozygosity is F. *mut*, mutated; N, normal; T, tumour; *WT*. wildtype. After Ref. 11, with permission.

polymorphisms (STRP), which are distributed approximately every 100,000 bp throughout the human genome. These microsatellites contain small dinucleotide or trinucleotide repeat units, the number of which may differ between the two alleles in a particular person. Microsatellite markers are now available which map thousands of these sequences to chromosomal loci. When DNA sequences containing these microsatellite markers are amplified by PCR in a person heterozygous for that particular microsatellite, the PCR will yield two products of different lengths, which can be resolved on an electrophoretic gel. Where amplification of tumour DNA from such a subject yields only one product, the tumour is said to show LOH, implying allelic loss. Persons who are homozygous for a particular marker are said to be noninformative for that marker. The concept of examining the variation and extent of allelic deletion in tumours was introduced by Vogelstein in an analysis of colorectal carcinomas and termed allelotyping.[13] Allelotypes generated in this fashion have identified several areas of frequent allelic deletion from which some of the responsible tumour suppressor genes have been cloned or identified. The most common areas of loss in HNSCC are at chromosome 9p21, 17p21, 13q14, 4p, 5q21 and several discrete regions on 3p and 8p.[14,15]

Inactivation of genes and oncogenic transformation

Allelic deletion is only one mechanism by which a copy of a gene can be inactivated. As there are two copies of each gene, inactivation of the gene requires inactivation of both copies of the gene, 'the second hit'. This may occur as a result of a genetic mutation or transcriptional silencing. Conversely, a protooncogene may be converted into an oncogene by a simple increase in the copy number of the gene (gene amplification) resulting in an overproduction of protein or by point mutations that affect the control of protein activity.

Not all mutations result in alteration in function of a gene. DNA mutation may occur as a result of base substitutions, as well as nucleotide insertions and deletions. Insertions and deletions of nucleotides are very rare in coding DNA, but if they occur they may produce a shift in the 'reading frame' which dramatically alters the