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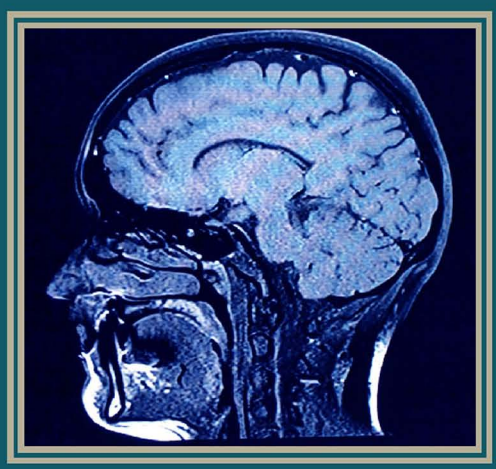
Scott-Brown's Otorhinolaryngology Head & Neck Surgery



VOLUME 1

Basic Sciences
Endocrine Surgery
Rhinology

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Scott-Brown's

EIGHTH EDITION

Otorhinolaryngology Head and Neck Surgery

VOLUME 1

Basic Sciences, Head and Neck Endocrine Surgery, Rhinology

VOLUME 2

Paediatrics, The Ear, Skull Base

VOLUME 3

Head and Neck Surgery, Plastic Surgery

Scott-Brown's Otorhinolaryngology Head and Neck Surgery

EIGHTH EDITION

VOLUME 1

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Foreword

The eighth edition of *Scott-Brown* signals the beginning of a new and exciting era for ear, nose and throat surgeons, and also the end of 10 years of very hard work undertaken by John Watkinson and Ray Clarke, the Editors-in-Chief, their team of subeditors and, not least, the publishers. Whatever subspeciality the current generation of trainees decides to follow, they will all have to read and refer to *Scott-Brown* in order to complete their education and gain accreditation. It will be a constant companion and guide throughout their professional lives.

When asked to write the foreword for this edition, I was immediately reminded that I had read John Ballantyne and John Groves's third edition as a trainee, bought the fourth edition as a senior registrar, written chapters for Alan Kerr and Philip Stell in the fifth edition, edited the *Basic science* volume of the fifth edition and was ultimately Editor-in-Chief of the seventh edition. As each edition takes about 10 years to produce, that makes me very old indeed. John and Ray have one final task as Editors-in-Chief: to recommend their successors to the publishers. That was made easy for me as both of them had proved themselves more than capable with the previous edition, and the eighth edition is now their masterpiece. They can enjoy the next 10 years as thousands of surgeons worldwide recognize and thank them for their industry.

This edition reflects the continued expansion of our speciality into fields that Scott-Brown himself could never have imagined. It lays the groundwork for the current generation to make their contribution that will, no doubt, be prompted by technological developments, an evidence base of what is wise and what is not, together with the experience gained by teamwork with other clinicians in today's multidisciplinary approach to patient care.

Simply looking at the table of contents it is clear to see that our role in endocrine surgery has increased dramatically over the last 10 years. The thyroid and parathyroids now account for 30 chapters. How would Scott-Brown have viewed that when the tonsils and adenoids justify just one chapter each, and the sore throat has a mere passing reference? Times have certainly changed and ENT surgery has grown up. We have reflected on our past practices, and the evidence base for our management protocols that was emphasized in the previous edition of *Scott-Brown* has been taken to heart.

I hope that this edition will find its way into every medical library in the world and onto every ENT surgeon's bookshelf. It will serve and guide surgeons throughout the English-speaking world, whether they live in high- or low-income countries. It is said that the tragedy of getting old is that we feel young. Reading these volumes makes me wish that I had my time all over again.

Michael Gleeson

Preface

When we were asked to head up the editorial team for this, the eighth edition of *Scott-Brown*, we were mindful of Michael Gleeson's towering achievement in bringing the seventh edition to fruition. Michael delivered a much-loved text – conceived in the early post-war years when antimicrobials, the operating microscope and the National Health Service were all in their infancy – in an entirely new format that befitted modern surgical scholarship. Authors, editors and readers alike had become acutely conscious of the need to quote high-quality evidence to guide clinical decisions; the concept of grading clinical recommendations – and, by implication, acknowledging gaps in the evidence base of our practice – was born. Recognizing the enormity of Michael's contribution led us into the trap that has befallen every editor who has come before us; we grossly underestimated the task ahead. We had misjudged the pace of change. What began as an 'update' of some outdated chapters became a complete rewrite to reflect the advances that marked the decade between editions, but we were determined to keep the text to a manageable size! In the end, we have 330 chapters, but with a slightly smaller page count than the seventh edition.

The basic science knowledge that underpins our clinical practice is no longer focused just on anatomy and physiology; genetics, molecular biology, new techniques for auditory implantation, information technology, new medical therapies for many old disorders together with seismic changes in endoscopic technology and in medical imaging have transformed our specialty. Today's head and neck surgery would have been unrecognizable to the early authors and editors. Surgical oncologists have recourse to completely different treatment strategies than did their predecessors and now work as part of multidisciplinary teams. They deal with different disease patterns and vastly changed patient expectations. Thyroid and parathyroid surgery has become almost exclusively the domain of the otolaryngologist. Surgery of the pituitary fossa has come within our ambit, as has plastic and reconstructive surgery of the head and neck as well as aesthetic facial surgery. Neurotology, audio-vestibular medicine, rhinology and paediatric otolaryngology are accepted subspecialties, each with its own corpus of knowledge and skills and each warranting a sizeable section of this text. Contemporary otolaryngology is now a collection of subspecialty interests linked by common 'stem' training and a shared passion for looking after patients with disorders of the upper respiratory tract and the head and neck.

There is a view that a single text – even a multivolume tome of this size – cannot cover the entire knowledge base of modern clinical practice. The subspecialist will, of course, need recourse to supplementary reading. The pace of change shows no sign of slowing down, but there is still a need for a comprehensive working text embracing the whole spectrum of our workload. That was the task we set our authors and section editors; we think they have done our specialty proud.

In the new 'digital' editorial world authors create manuscripts on personal computers. They transmit chapters, figures, amendments and revisions across continents and time zones with a few keystrokes. The bulky packages containing grainy photographic prints and the reams of paper with closely-typed and heavily scored text that accumulated on authors' and editors' desks are a distant memory. References, guidelines and systematic reviews are all available online; the editorial 'red pen' has been replaced by a cursor on the screen. This 'new age' has enabled us to look ever further for expertise. We are proud to have enlisted the support of authors from more than 20 countries for this edition. *Scott-Brown* always enjoyed particular affection and respect in Asia, Australia, Africa and the Middle East. It has been a joy to welcome authors in increasing numbers from many of these parts of the world. We are now a truly global specialty and the eighth edition fully reflects this.

What has not changed is the huge time commitment authors and editors need to make. That time now has to be fitted into an increasingly pressurized work environment. Revalidation, mandatory training, more intense regulatory scrutiny, expanding administrative burdens and ever-expanding clinical commitments leave little time for scholarship. Our section editors are all busy clinicians. They have generously given their time, first instructing authors, cajoling them and then editing their chapters, virtually all of which have been completely rewritten since the last edition. Each author was chosen because of his or her specific clinical and scientific expertise and none has disappointed. Authors and section editors receive no reward other than the satisfaction of knowing that they have made a contribution to teaching and learning in a specialty that has given us all so much professional satisfaction. We are profoundly grateful to them and hope that their endeavours spur the next generation of otolaryngologists to carry on this noble tradition. *Scott-Brown* simply wouldn't happen without this generous and dedicated commitment, unstintingly and graciously given.

It is impossible to produce a book like *Scott-Brown* without the contribution of many individuals working behind the scenes. We would like to express our gratitude to our Publishers, Taylor and Francis, and to the staff who have worked on this project from its early days in 2011 to publication in 2018. In particular we would like to mention Cheryl Brandt who with good humour and patience helped to reel in many of the 330 chapters. Miranda Bromage joined the team in 2016 and her publishing experience and enthusiasm for medical education have helped guide this new edition through its final phases to publication. Finally, we are indebted to Nora Naughton who has dedicated so much more than just her extensive publishing skills to this project. Nora's meticulous attention to detail, combined with her warmth and wisdom have encouraged us all at the end of this endeavour.

We are truly 'passing on the torch' of a huge amount of accumulated knowledge and wisdom; it is this that gives us, the Editors-in-Chief, the greatest pleasure.

Read on and enjoy, our thoughts are yours.

RWC
JCW

I wish to acknowledge the love, happiness and inspiration that have been passed on to me by both my parents and grandparents. I recognize and value the friendship of my dear friend Ray Clarke who has been with me all the way on this rewarding and worthwhile endeavour. I would specifically like to thank Esme, Helen and William, without whom none of this would have been achievable. Their love and support has helped guide me through the years leading up to the publication of this tome, and my final thanks go to Angela Roberts and Sally Holden for their typing and editing skills.

JCW 2018

Thanks to my wife Mary for her patience and support. My parents, Emmet and Doreen Clarke, both sadly died during the preparation of this book. They would have been proud to have played a part in such a scholarly enterprise.

RWC 2018

Black Hut on the River Test – Pastel by W G Scott-Brown – circa 1970. Reproduced by kind permission of Mr Neil Weir, who was presented with the original by the artist.

A Tribute to Bill Scott-Brown

Walter Graham ('Bill') Scott Brown. 1897–1987

Walter Graham ('Bill') Scott-Brown was twenty-three when he arrived at Corpus Christi College Cambridge in 1919. One of the generation of young men whose entry to university and the professions was delayed by their participation in the First World War, he had joined the Gunners in 1915 as an 18-year-old. He considered himself blessed to have survived – although wounded – when so many of his contemporaries never returned from the Front. In those early post-WW1 years the medical school at St Bartholomew's ('Barts') in London was keen to attract 'gentlemen'. To this end a series of scholarships – 'Shuter's scholarships' – was established to lure those with humanities degrees from Oxford and Cambridge into medicine. It was via this scheme that the young Scott-Brown qualified MB, BCh in 1925. By now married to Margaret Bannerman, one of the very few women medical graduates of her generation, the two established a general practice in Sevenoaks, Kent. His work here involved looking after children with poliomyelitis, which was then commonplace, and his MD thesis was on polio-related bulbar palsy. It earned him the Copeman Medal for research from the University of Cambridge. While working in general practice, Bill pursued his interest in the then fledgling specialty of otolaryngology, securing fellowships from London and Edinburgh. Postgraduate training was haphazard; there were no structured programmes or even junior posts, so the young Scott-Brown was fortunate to be awarded a Dorothy Temple Cross Travelling Fellowship. Mrs Florence Temple Cross had set up these awards (now administered by the Medical Research Council) in memory of her daughter, who died in 1927 aged thirty-two. They were made available to young physicians to help them travel to overseas centres specifically to study tuberculosis, then rampant and one of the commonest causes of death in young adults. The young Scott-Brown visited the leading pioneers of the day in Berlin, Vienna, Budapest, Stockholm, Copenhagen, Madrid and Venice. Here he developed his considerable endoscopy skills. He reported that his first bronchoscopies were done on a Venetian street entertainer who, for a few coins, would inhale sundry objects that the doctors would then dexterously retrieve from his main stem and segmental bronchi – without of course any anaesthesia!

Times were lean on Scott-Brown's return. Margaret ('Peggy') was now a popular and well-established GP who supported him as his private practice developed. Eventually he secured appointments at East Grinstead, the Royal National and Royal Free Hospitals. He had a thriving Harley Street practice and was the favoured otolaryngologist of the aristocracy. His reputation was such that he become laryngologist to the Royal family, was appointed Commander of the Victorian Order and was a particular favourite of the then Princess Royal, HRH Mary the Countess of Harewood.

By 1938 he was wealthy enough to purchase a farm in Buckinghamshire where he bred prize-winning shorthorn cattle. Ironmongery and blacksmith work were hard to come by during the war years, so Scott-Brown prided himself on his ability to make his own agricultural implements, cartwheels and farm wagons in a makeshift forge he himself established on the farm. He would while away endless hours here at weekends following a busy week in London. An accomplished fly fisherman, he was part of the exclusive Houghton Club whose members fished the River Test in Hampshire, where he numbered aristocrats including the Prince of Wales among his circle.

Scott-Brown's celebrated textbook came about in the early 1950s, when he became ill with jaundice and heart trouble. He was advised to rest, and took 6 months off work. Not satisfied with editing what has become the standard UK textbook, he took up painting as well. He became a celebrated artist whose work is still prized in many private collections. One of his pastels is reproduced on the preceding page.

Bill Scott-Brown lived to be 90. He died in July 1987, six weeks after his beloved Peggy and just as the fifth edition of the celebrated textbook that still bears his name was going to press. His legacy lives on in the pages of this book, and we are proud to continue the tradition of scholarship and learning which he established all those years ago.

We would like to thank Martin Scott-Brown for his help in compiling the biography above.

John C. Watkinson and Raymond W. Clarke
London, 2018

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Chapter 1, Molecular biology, contains some material from 'Molecular biology' by Michael Kuo and Richard M Irving. The material has been revised and updated by the current author.

Chapter 3, Gene therapy, contains some material from 'Gene therapy' by Scott M Graham and John H Lee. The material has been revised and updated by the current author.

Chapter 5, Radiotherapy and radiosensitizers, contains some material from 'Radiotherapy and radiosensitizers' by Stewart G Martin and David AL Morgan. The material has been revised and updated by the current author.

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Chapter 46, Optical coherence tomography, contains some material from 'Optical coherence tomography' by Mariah Hahn and Brett E Bouma. The material has been revised and updated by the current author.

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Chapter 109, Granulomatous conditions of the nose, contains some material from 'Granulomatous conditions of the nose' by David J Howard and Valerie J Lund. The material has been revised and updated by the current author.

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Abbreviations

1,25-DHCC	1,25 dihydroxycholecalciferol
2D	two-dimensional
3D	three-dimensional
4D CT	four-dimensional computed tomography
5-FdUMP	5-fluoro-2 deoxyuridine monophosphate
5-FU	5-fluorouracil
5-FUMP	5-fluorouridine monophosphate
6MP	6-mercaptopurine
18-FDG	2-18-fluoro-2-deoxy-D-glucose
A	adenine; *or* anterior
AACE	American Association of Clinical Endocrinologists
AAES	American Association of Endocrine Surgeons
AAGBI	Association of Anaesthetists of Great Britain and Ireland
AAOHNS	American Academy of Otolaryngologists/ Head and Neck Surgeons
AAV	adeno-associated virus
ABBA	axillo-bilateral-breast approach
ABG	arterial blood gas
ABPA	allergic bronchopulmonary aspergillosis
ABR	auditory brainstem response
ABRS	acute bacterial rhinosinusitis
AC	air conduction; *or* alternating coupled; *or* adenylate cyclase
ACE	angiotensin-converting enzyme
ACGME	Accreditation Council for General Medical Education
ACh	acetylcholine
AchR	acetyl choline receptor
ACR	Americal College of Rheumatology
ACT	Aid for Children with Tracheostomies
ACTH	adrenocorticotrophic hormone
AD	Alzheimer's disease
ADAM-33	A disintegrin and metalloprotease 33k
ADC	apparent diffusion coefficient
ADCC	antibody-dependent cellular cytotoxicity
ADH	antidiuretic hormone
ADP	adenosine diphosphate
ADR	adverse drug reaction
ADU	avoidable, delayed or undertransfusion
Ad-VEGF	adenovirus-encoding vascular endothelial growth factor
AEA	anterior ethmoidal artery
AED	aerodynamic equivalent diameter
AEF	auditory-evoked cortical magnetic field
AERD	aspirin-exacerbated respiratory disease
AES	assigned educational supervisors
AF	atrial fibrillation; *or* anterior fontanelle
AFAP	attenuated familial adenomatous polyposis
AFIP	Armed Forces Institute of Pathology
AFOI	awake fibre-optic intubation
AFRS	allergic fungal rhinosinusitis
AFU	angiofollicular unit
AGHDA	Assessment of Growth Hormone Deficiency in Adults
AH	adenohypophysis
AICA	anterior inferior cerebellar artery
AIDS	acquired immunodeficiency syndrome
AIFR	acute invasive fungal rhinosinusitis
AIFS	acute invasive fungal sinusitis
AIH	amiodarone-induced hypothyroidism
AIP	aryl hydrocarbon receptor-interacting protein
AIT	amiodarone-induced thyrotoxicosis
AJCC	American Joint Committee on Cancer
AKT	serine/threonine kinase
ALLO	alloimmunization
ALTB	acute laryngotracheobronchitis
ALS	advanced life support; *or* amyotrophic lateral sclerosis; *or* acid labile subunit
ALSPAC	Avon Longitudinal Study of Parents and Children
ALTB	acute laryngotracheobronchitis
AML	acute myeloid leukaemia
AMR	antimicrobial resistance
AN	acoustic neuroma; *or* auditory neuropathy; *or* audiovestibular nerve
ANA	anti-nuclear antibody
AN/AD	auditory neuropathy/auditory dyssynchrony
ANCA	antineutrophil cytoplasmic antibody
ANSD	auditory neuropathy spectrum disorder
ANTS	anaesthetists' non-technical skills
AOM	acute otitis media
AON	anterior olfactory nucleus
AP	anterior–posterior; *or* action potential
APACHE	acute physiology and chronic health evaluation
APC	antigen presenting cell; *or* activated protein C; *or* argon plasma coagulation; *or* adenomatous polyposis coli

APIT activated partial thromboplastic time
APOF aggressive psammomatoid ossifying fibroma
APTT activated partial thromboplastin time
AQP2 aquaporin 2
ARIA allergic rhinitis and its impact on asthma
ARR absolute risk reduction
ARS acute rhinosinusitis
ARSAC Administration of Radioactive Substances Advisory Committee
ART advanced rotating tomograph; *or* antiretroviral therapy
ARIA allergic rhinitis and its impact on asthma
ARS acute rhinosinusitis
ASA aspirin-induced asthma; *or* aspirin-sensitive asthma; *or* American Society of Anesthesiologists
a-SCC anterior semicircular canal
AT ataxia telangiectasia; *or* auditory therapy or training; *or* autotransplantation
ATA American Thyroid Association
ATC anaplastic thyroid carcinoma; *or* air traffic control
ATD ascending tract of Deiters; *or* adult therapeutic dose
ATIII antithrombin III
ATP adenosine triphosphate
ATR acute transfusion reaction
AVP arginine vasopressin
AW anterior wall

BABA bilateral axillo-breast approach
BAC bacterial artificial chromosome
BADS British Association of Day Surgery
BAES British Association of Endocrine Surgeons
BAETS British Association of Endocrine and Thyroid Surgeons
BAT basophil activation test
BCHD bone conduction hearing device
BCP biphasic calcium phosphate
BCSH British Committee for Standards in Haematology
BD Behcet's disease
BDP beclomethasone dipropionate
BFU-E burst-forming unit erythroid
BiPAP bilevel positive airway pressure
BIPP bismuth and iodoform paraffin paste
BIS bispectoral index
BL Burkitt's lymphoma
BMA British Medical Association; *or* bone marrow aspirate
BMD bone mineral density
BMI body mass index
BMP bone morphogenetic protein; *or* bone morphogenic protein
BOR brachio-oto-renal; *or* branchioterenal syndrome
BP blood pressure
BPE bilateral parathyroid exploration
BSAC British Society for Antimicrobial Chemotherapy
BTA British Thyroid Association

C cytosine
CAD caspase-activated DNase
CAF carcinoma-associated fibroblasts
CAG curriculum advisory group
cAMP 3',5'-monophosphate
CAP compound action potential; *or* category of auditory performance; *or* College of American Pathologists
CAPS cryopyrin-associated periodic syndromes
CARD caspase recruitment domain
CaSR calcium-sensing receptor
CASTLE carcinoma with thymus-like elements
CBD case-based discussion
CBF ciliary beat frequency
CCD charge-coupled device
CCH C-cell hyperplasia
CCP cyclic citrullinated peptide
CCR chemokine receptor
CCT Certificate of Completion of Training
CD cluster of differentiation; *or* colloid droplets; *or* compact disk; *or* Cowden's disease
CDA cold dry air
CDAD *C. difficile* associated diarrhoea
CDC Centers for Disease Control and Prevention
CDI *C. difficile* infection
CDK cyclin-dependent kinase
CEA carcinoembryonic antigen
CEFTE carcinoma of the thyroid with Ewing family tumour elements
CEPOD Confidential Enquiry into Perioperative Deaths
CER control event rate
CESR Certificate of Eligibility for Specialist Registration
CEX clinical evaluation exercises
CF cystic fibrosis; *or* characteristic frequency
CFD colour-flow duplex Doppler; *or* computational fluid dynamics
c-FOS fos proto-oncogene

CFTR cystic fibrosis transmembrane conductance regulator
CG clinical governance
CGD chronic granulomatous disease
CGH comparative genomic hybridization
CGIFS chronic granulomatous invasive fungal sinusitis
CGRP calcitonin gene-related peptide
CHI Commission for Healthcare Improvement (UK)
CHOP-R cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab
CI cochlear implant; *or* cardiac index; *or* confidence interval; *or* concha inferior
CICV can't intubate can't ventilate
CIFR chronic invasive fungal rhinosinusitis
CIFS chronic invasive fungal sinusitis
CINCA chronic infantile neurologic cutaneous articular syndrome
CJD Creutzfeldt–Jakob disease
CK cytokeratin
CKD-MBD chronic kidney disease mineral bone disorder
CLL chronic lymphatic leukaemia; *or* chronic lymphocytic leukaemia
CM concha media; *or* cochlear microphonic; *or* cricothyroid muscle
CMAP compound muscle action potential
CML chronic myeloid leukaemia
CMSO complementary metal oxide detectors
CMT Charcot—Marie—Tooth; *or* combined modality therapy
CMV cytomegalovirus
CN cranial nerve; *or* cochlear nuclei; *or* cochlear nerve
CNS central nervous system
CO_2 carbon dioxide
CoAA coactivator AA
COF cemento-ossifying fibroma
COMET Core Outcomes Measures in Effectiveness Trials
CONSORT Consolidated Standards of Reporting Trials
COPD chronic obstructive pulmonary disease
COSI Client Oriented Scale of Improvement
COX-2 cyclo-oxygenase 2
CPA cerebellopontine angle
CPAP continuous positive airway pressure
CPD citrate phosphate dextrose; *or* continuing professional development
CPG central pattern generator
CRC colorectal cancer
CRD component resolved diagnostics
CREB cAMO binding element
CREST calcinosis, Raynaud's, oesophageal involvement, sclerodactyly, telangiectasis
CRF corticotrophin-releasing factor
CRH corticotrophin-releasing hormone
CRH-R corticotrophin releasing hormone receptor
CRP C-reactive protein; *or* canalith repositioning procedure
CRS chronic rhinosinusitis; *or* congenital rubella syndrome
CRSwNP chronic rhinosinusitis with nasal polyps
CRSsNP chronic rhinosinusitis without nasal polyps
CRS chronic rhinosinusitis; *or* congenital rubella syndrome
CS corticosteroid; *or* cell salvage and autologous transfusions
CSC cancer stem cells
CSF cerebrospinal fluid
CSS Churg-Strauss syndrome
CST core surgical training
CT computed tomography; *or* conventional thyroidectomy
CTA composite tissue allograft; *or* computed tomography angiography
CTLA cytotoxic T-lymphocyte-associated antigen
CTM cricothyroid membrane
Cu-ATSM Cu(II)-diacetyl-bis-N4-methylthiosemicarbozone

DA double adenoma
DACH diaminocyclohexane
DAHANCA Danish Head and Neck Cancer Study
DAMPs damage-associated molecular pattern molecules
DAS Difficult Airway Society
DAT direct antiglobulin test
DAVF dural arteriovenous fistulas
dB decibel
DBM demineralized bone matrix
DCE MRI dynamic contrast-enhanced MRI
DCR dacryocystorhinostomy
DD death domain
DDAVP desmopressin
DDE Doctrine of Double Effect
DED death effector domain
DFN3 deafness type 3
DFO-H deferoxamine-hespan
DHI dizziness handicap inventory
DHTR delayed haemolytic transfusion reaction
DI diabetes insipidus
DIC disseminated intravascular coagulation
DIO deiodinases

DISC death inducing signal complex
DIT diiodotyrosine; *or* di-iodothyronine
DLBCL diffuse large B-cell lymphoma
DM diabetes mellitus; *or* decision making
DMARDS disease-modifying anti-rheumatic drugs
DMSA dimercapto succinic acid
DMSO dimethylsulfoxide
DNA deoxyribonucleic acid
DNAR do not attempt resuscitation
dNTP deoxynucleoside triphosphate
DOAC direct oral anticoagulant
DOHNS Diploma in Otolaryngology – Head and Neck Surgery
DOPS direct observation of procedural skills
DPA Data Protection Act (UK)
DPOAE distortion product otoacoustic emission
DR death receptor; *or* drug resistance
DSA digital subtraction angiography
dsRNA double-stranded RNA
DTC differentiated thyroid cancer
DTD DT-diaphorase
dTMP deoxythymidine monophosphate
dUMP deoxyuridine monophophase
DVT deep vein thrombosis
DWI diffusion weighted image

EAACI European Academy of Allergology and Clinical Immunology
EAC external auditory canal; *or* external acoustic canal
EAL ethmoidal artery ligation
EAT endoscopic-assisted thyroidectomy
EBM evidence-based medicine
EBNA Epstein–Barr virus-associated nuclear antigen
EBP evidence-based practice
EBRT external beam radiotherapy
EBSLN external branch of the superior laryngeal nerve
EBUS endobronchial ultrasound
EBV Epstein–Barr virus
ECA external carotid artery
ECAL external carotid artery ligation
ECG electrocardiogram
ECM extracellular matrix
ECMO extracorporeal membrane oxygenation
ECochG electrocochleography
ECog electrocochleogram
ECOG Eastern Cooperative Oncology Group (USA)
ECP eosinophil cationic protein; *or* extra corporeal perfusion
ECS extracapsular spread
EDTA ethylenediaminetetraacetic acid
EEA endoscopic endonasal approach
EEG electroencephalography; *or* electroencephalogram
EER experimental event rate
EFRS eosinophilic fungal rhinosinusitis
EFVPTC encapsulated follicular variant of PTC
EGF epidermal growth factor
eGFR estimated glomerular filtration rate
EGFR epidermal growth factor receptor
ELISA enzyme-linked immunosorbent assay
EMG electromyography
EMT epithelial-mesenchymal transition
EMRS eosinophilic mucin rhinosinusitis
ENA extractable nuclear antigen
ENoG electroneurography
ENS empty nose syndrome
ENT ear, nose and throat
EORTC European Organisation for Research and Treatment of Cancer
EPO erythropoietin
EPOS European position paper on rhinosinusitis and nasal polyps
EQ-5D EuroQol
ER enhancement ratio; *or* endoplasmic reticulum
ERα oestrogen receptor alpha
ERAS enhanced recovery after surgery
ERK extracellular signal-regulated kinase
ERS European Rhinological Society
ES embryonic stem; *or* endolymphatic sac
ESBL extended spectrum β-lactamase
ESPAL endonasal ligation of the sphenopalatine artery
ESR erythrocyte sedimentation rate
ESS endoscopic sinus surgery; *or* Epworth Sleepiness Scale; *or* empty sella syndrome
ET-1 endothelin-1
ETE extrathyroidal extension
ETT endotracheal tube
EUA examination under anaesthesia
EUCAST European Committee on Antimicrobial Susceptibility Testing
EVAL ethylene-vinyl alcohol copolymer
EWTD European Working Time Directive

Fab fragment antigen binding
FACT functional assessment of cancer therapy
FADD Fas-associated death domain

Fas-L Fas ligand
FBC full blood count
Fc fragment crystallizable
FcεRI high affinity IgE receptors
FD fibrous dysplasia
FDA Food and Drug Administration (USA)
FDG fluorodeoxyglucose; *or* 2-[18F] fluoro-2-deoxy-D-glucose; *or* F18-fluoro-2-deoxy-D-glucose
FD-OCT fourier domain optical coherence tomography
FDG-PET 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography; *or* fluorine-18-labelled deoxyglucose positron emission tomography
FE frontal ethmoidal cell
FEA finite element analysis
FESS functional endoscopic sinus surgery
FEIBA factor VIII inhibitor bypassing agent
F-ETNIM fluorine-18 fluoroerythronitroimidazone
FFP fresh frozen plasma
FGF fibroblast growth factor
FHH familial hypocalciuric hypercalcaemia
FIHP familial isolated hyperparathyroidism
FiO2 fraction of inspired oxygen
FIPA familial isolated pituitary adenomas
FISH fluorescence *in situ* hybridization
FITS functional inferior turbinosurgery
FIV feline immunodeficiency virus
FLAIR fluid attenuated inversion recovery
FMF familial Mediterranean fever
FMISO fluorine-18 fluoromisonidazole
fMRI functional magnetic resonance imaging
FMTC familial medullary thyroid cancer
FN facial nerve
FNA fine-needle aspiration/aspirate
FNAB fine-needle aspiration biopsy
FNAC fine-needle aspiration cytology
FNHTR febrile non-haemolytic transfusion reactions
FOI fibreoptic orotracheal intubation
FRS fungal rhinosinusitis
FS folliculostellate; *or* frontal sinus
FSH follicle-stimulating hormone
fT3 free T3
fT4 free T4
FTC frequency threshold curve; *or* follicular thyroid carcinoma
FT-UMP follicular tumour of uncertain malignant potential
FVPTC follicular variant of papillary thyroid carcinoma

G guanine
GABA gamma-aminobutyric acid
GABHS group A beta-haemolytic streptococcus
GAG glycosaminoglycan
GBI Glasgow Benefit Inventory
GBM anti-glomerular basement membrane
GC glucocorticoid
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
GHRP growth hormone-releasing peptide
GI gastrointestinal
GMC ganglion mother cell; *or* General Medical Council (UK)
GM-CSF granulocyte-macrophage colony stimulating factor
GMS Gomori's methamine silver stain
GnIH gonadotrophin inhibitory hormone
GnRH gonadotrophin-releasing hormone
GORD gastro-oesophageal reflux disease
gp glycoprotein
GP general practitioner
GPA granuloma; *or* granulomatosis with polyangitis
G protein guanine nucleotide-binding regulatory protein
GRADE Grading of Recommendation, Assessment, Development and Evaluation
GRB2 growth factor receptor binding protein 2
Gs G-protein adenylate cyclase stimulator
GSH glutathione
GSP stimulatory G protein
GTN nitroglycerin
GTR guided tissue regeneration
GTV grow tumour volume
GvHD graft-versus-host disease

HA hydroxyapatite
H&E haematoxylin and eosin
H&N head and neck
H2 histamine receptor type 2
HA hydroxyapatite
HAART highly active antiretroviral therapy
HAI hospital-acquired infection
HBME-1 mesothelium-associated antibody
Hb haemoglobin
HbA adult haemoglobin

HBO hyperbaric oxygen
HBOT hyperbaric oxygen therapy
HCG human chorionic gonadotrophin
HD haemodialysis
HDL high-density lipoprotein
HDM house dust mite
HDU high dependency unit
He-Ne helium-neon
HEPA high-efficiency particulate air
HES hospital episode statistics
HFJV high-frequency jet ventilation
HFT hereditary familial telangiectasia
HGF hepatocyte growth factor
HH hypogonadotrophic hypogonadism
HHI Hearing Handicap Inventory; *or* hereditary hearing impairment
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
HIDS hyper-IgD syndrome
HIT heparin-induced thrombocytopenia
HIV human immunodeficiency virus
HL hearing loss; *or* hearing level; *or* hairy leukoplakia
HLA human leukocyte antigen
HLH haemophagocytic lymphohistiocytosis
HM history of migraine; *or* hemifacial microsomia
HMW high molecular weight
HMWC high molecular weight compound
HMWCK high molecular weight cytokeratin
HNSCC head and neck squamous cell carcinoma
Ho-YAG holmium yttrium aluminium garnet
HPA hypothalamic–pituitary–adrenal axis
HPC haemangiopericytoma
HPT hyperparathyroidism
HPT-JT hyperparathyroidism-jaw tumour
HPV human papillomavirus; *or* human herpes virus 8
HPZ herpes zoster
HR hazard ratio
HRA Human Rights Act
HRQOL health-related quality of life
HR heart rate
HRT hormone replacement therapy
HRV rhinoviruses
HSC haematopoietic stem cell
HSCT haemopoietic stem cell transplant
HSD hydroxysteroid dehydrogenase enzyme
HSE handling and storage errors
HSV herpes simplex virus
HSV-1 herpes simplex virus type 1
HSV-2 herpes simplex virus type 2
HSV-TK herpes simplex thymidine kinase
HTA hyalinizing trabecular adenoma; *or* Health Technology Assessment
hTERT human telomerase reverse transcriptase
HTR haemolytic transfusion reaction
HTT hyalinizing trabecular tumours
HU Hounsfield unit
HUI Health Utilities Index
HVDT health visitor distraction test
Hz hertz
HZV herpes zoster virus

IAC internal auditory canal
IAR intermittent allergic rhinitis
IBCT incorrect blood component transfused
ICA internal carotid artery
ICAD inhibitor caspase-activated DNase
ICAM intercellular adhesion molecule
ICAM-1 intercellular adhesion molecule 1
ICD International Classification of Disease
ICF International Classification of Functioning
ICS intra-operative cell salvage
ICU intensive care unit
IDD intracellular death domain
IDT infant distraction test; *or* intra-dermal test
IFN interferon
IFN-α interferon-alpha
IFN-β inteferon-beta
IFN-γ interferon-gamma
IFVPTC invasive follicular variant of PTC
Ig immunoglobulin
IGD isolated GnRH-deficiency
IgE immunoglobulin E
IGF insulin-like growth factor
IGF-I insulin-like growth factor 1
IGF-II insulin-like growth factor II
IGFBP insulin-like growth factor binding protein
IgG immunoglobulin G
IgGκC immunoglobulin G kappa chain
IGS image-guided surgery
IHC immunohistochemistry; *or* inner hair cell
IIT iodide-induced thyrotoxicosis

IJV internal jugular vein
IL interleukin
IL-1 interleukin-1
IL-2 interleukin-2
IL-3 interleukin-3
IL-5 high interleukin
IL-6 interleukin-6
ILMA intubating laryngeal mask airway
i.m. intramuscular
IMA internal maxillary artery
IMAL internal maxillary artery ligation
IMF intermaxillary fixation
IMP importin
IMRT intensity-modulated radiation therapy
iNOS inducible nitric oxide synthase
INR international normalized ratio; *or* interventional neuroradiology
IOM institute of Medicine
IONM intra-operative neural/nerve monitoring
IOPTH intra-operative PTH
IOQPTH intra-operative quick assay of intact parathyroid hormone
IOUS intra-operative ultrasound scanning
IP Inverted papilloma
IPD invasive pneumococcal disease
iPSCs induced pluripotency stem cells
IPSS inferior petrosal sinus sampling
IRI ischaemia-reperfusion injury
IRS insulin receptor substrate; *or* Intergroup Rhabdomyosarcoma Study
ISAAC International Study of Asthma and Allergies in Childhood
ISCP International Surgical Curriculum Programme
ISL *in situ* ligation
IT inferior turbinate
ITA inferior thyroid artery
ITAM immunoreceptor tyrosine-based activation motif
ITP idiopathic thrombocytopenic purpura
ITU intensive therapy unit
i.v. intravenous
IVIg intravenous immunoglobulin

JAK2 Janus kinase 2
JCST Joint Committee on Surgical Training
JIA juvenile idiopathic arthritis
JLNS1 Jervell and Lange-Nielsen syndrome
JNA juvenile nasopharyngeal angiofibroma
JNK c-Jun N-terminal kinase

K Kirschner
KCCT kaolin cephalin clotting time
KDOQI Kidney Disease Quality Outcomes Initiative
keV kilo electron volt
KOH potassium hydroxide solution prep test
KISS-R kisspeptin receptor (also known as GR54)
KS Kaposi's sarcoma
KTP potassium titanyl phosphate

LA lymphangioma
LAR local allergic rhinitis
LAT lateral aberrant thyroid
LC1 livery cystolic 1
LCM laser capture microdissection
LDH lactate dehydrogenase
LDL low-density lipoprotein; *or* loudness discomfort level
LED light-emitting diode
LFA lymphocyte-function associated antigen
LFJV low-frequency jet ventilation
LH luteinizing hormone
LHB lateral-head-back
LH-R luteinizing hormone receptor
LINAC linear accelerator
LKM liver kidney microsomal
LM laryngeal mask
LMA laryngeal mask airway
LMW low molecular weight
LMWC low molecular weight compound
LMWH low molecular weight heparin
LOCR lateral opticocarotid recess
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
LP lamina papyracea; *or* lichen planus; *or* lymphocyte predominant
LPR laryngopharyngeal reflux; *or* late phase reactions
LR likelihood ratio
LR-OCT long-range optical coherence tomography
LTRA leukotriene receptor antagonists
LW lateral wall

M metastases
M2 Matrix 2 ion channels
MAb monoclonal antibodies
MABP mean arterial blood pressure
MAC membrane attack complex; *or* *Mycobacterium avium* complex

MAD mucosal atomization device
MAGE-3 melanoma-associated antigen-3
MALT mucosa-associated lymphoid tissue
MAOI monoamine oxidase inhibitor
MAP minimum audible pressure
MAPK mitogen-activated protein kinase
MAS mandibular advancement splint; *or* macrophage activation syndromes
MBL mannose-binding lectin
MC2R melanocortin 2 receptor
MCP monocyte chemotactic protein
MCS mental component summary
MCT medullary thyroid carcinoma
MCV mean corpuscular volume
MDCT multi-detector row CT
MDS myelodysplastic syndrome
MDT multidisciplinary team
ME middle ear
MEG magnetoencephalography
MEK MAPK/extracellular signal related kinase
MEN multiple endocrine neoplasia
MeSH medical subject heading
MET middle ear transducer
M-FISH multifluor FISH
MGHD multiple gland hyperplasia disease
MGO methylglyoxal
MGUS monoclonal gammopathy of uncertain significance
MHC major histocompatibility complex
MHP massive haemorrhage pack
MI myocardial infarction
mIBG metaiodobenzylguanidine; *or* iodine-123-metaiodobenzylguanidine
MIBI sestamibi; *or* technetium-99m
MIC minimum inhibitory concentration
μOCT micro-optical coherence tomography
MIFC minimally invasive follicular carcinoma
MIP minimally invasive parathyroidectomy; *or* maximum intensity projection; *or* macrophage inflammatory protein;
miRNA micro ribonucleic acid
MIST minimal invasive sinus techniques
MIT monoiodotyrosine; *or* mono-iodothyronine; *or* minimally invasive thyroidectomy
MIVAT minimally invasive video-assisted thyroidectomy
MLKL mixed lineage kinase domain-like protein
MLTB microlaryngotracheobronchoscopy
MMC mitomycin C; *or* Modernising Medical Careers
MMP mucous membrane pemphigoid; *or* matrixmetalloprotease
MMR measles, mumps and rubella
MNG multinodular goitre
MOCR medial opticocarotid recess
MODS multiple organ dysfunction syndrome
MOE malignant otitis externa
MOFT multiple oxyphil follicular tumour
MOS Medical Outcomes Study
MPA microscopic polyangiitis
MPTS Medical Practitioner's Tribunal Service
MPO myeloperoxidase
MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MR magnetic resonance
MRA magnetic resonance angiography
MRC Medical Research Council (UK)
MRCS Member of the Royal College of Surgeons
MRI magnetic resonance imaging
mRNA messenger ribonucleic acid
MRSA methicillin-resistant *Staphylococcus aureus*
MS multiple sclerosis
MSBOS maximum surgical blood ordering schedule
MSCs mesenchymal stem cells
MSF multi-source feeback
MSSA methicillin-susceptible strains
MT maxilloturbinal; *or* middle turbinate
MTC medullary thyroid carcinoma
mtDNA mitochondrial DNA
mTORC1 mammalian target of rapamycin 1
mTORC2 mammalian target of rapamycin 2
MW medial wall

N nodal
NADP nicotinamide adenine dinucleotide phosphate
NADPH reduced form of nicotinamide adenine dinucleotide phosphate
NANIPER non-allergic non-infectious perennial rhinitis
NAP4 Fourth National Airway Project
NARES non-allergic rhinitis with eosinophilia syndrome
NBCA n-butyl-2-cyanoacrylate; *or* N-butylcyanoacrylate
NBT nitro blue tetrazolium
NCAS National Clinical Assessment Service (UK)
NCEPOD National Confidential Enquiry into Patient Outcome Death (UK)
NCIC National Cancer Institute of Canada
ncRNA non-coding ribonucleic acid
Nd-YAG neodymium-yttrium aluminium garnet
NET nerve excitability test; *or* neuroendocrine tumour

NF1 neurofibromatosis type 1
NF2 neurofibromatosis type 2
NH normal hearing; *or* neurophypophysis
NHANES National Health and Nutrition Examination Survey
NHL non-Hodgkin's lymphoma
NHS National Health Service (UK)
NHSLA National Health Service Litigation Authority
NIBP automatic non-invasive blood pressure
NICE National Institute for Health and Care Excellence (UK)
NIFTP non-invasive follicular tumour with papillary-like nuclei
NIH National Institutes of Health (USA)
NIM nerve integrity monitor
NIPF nasal inspiratory peak flow
NIS Na+/I– symporter
NK natural killer
nLTP non-specific lipid transfer protein
NNT number needed to treat
NO nitric oxide
NO2 nitric dioxide
NOAC novel oral anticoagulant
NOE naso-orbito-ethmoid
NOTSS non-technical skills for surgeons
NOS not otherwise specified
NP nasopharynx; *or* nasopharyngeal
NPC nasopharyngeal cancer; *or* nasopharyngeal carcinoma
NPSA National Patient Safety Agency (UK)
NPT near patient testing
NPV negative predictive value
NRTIs nucleoside/nucleotide reverse transcriptase inhibitors
NSAID non-steroidal anti-inflammatory drug
NSF national service framework; *or* nasoseptal flap
NSHI non-syndromic hearing impairment
NTT near-total thyroidectomy

O3 ozone
OAE otoacoustic emission
OB olfactory bulb
OCT optical coherence tomography
ODP operating department practitioner
OF ossifying fibroma
OFDI optical frequency domain imaging
OIDA observe; interpret; decide; act
OMC ostiomeatal complex
OPC oropharyngeal cancer; *or* oropharyngeal candidiasis
OPCS Office for Population Censuses and Surveys (UK)
OPF osteoplastic flap procedure
OR occupational rhinitis
OREP olfactory event-related potential
ORL otorhinolaryngology
OSA obstructive sleep apnoea
OSATS obstructive structured assessment of technical skill
OTOF otoferlin
OXTR oxytocin receptor

P phosphate; *or* posterior
PA pernicious anaemia
PAC P1 artificial chromosome; *or* pulmonary artery catheter; *or* parathyroid carcinoma
PACS picture archiving and communication systems
PACU post-anaesthesia care unit
PAF platelet-activating factor
PBA procedure-based assessment
PBP progressive bulbar palsy
PCA patient-controlled analgesia
PCC prothrombin complex concentrate; *or* Professional Conduct Committee (UK); *or* pheochromocytoma
PCD primary ciliary dyskinesia
PCOS polycystic ovary syndrome
PCR polymerase chain reaction
PCS physical component summary
PD Parkinson's disease
PDCAT poorly differentiated carcinoma of the thyroid
PDE phosphodiesterase
PD1 programmed cell death protein 1
PDGF platelet-derived growth factor
PDL pulsed dye laser
PDR Physicians' Desk Reference
PDS polydimethylsiloxane
PDT photodynamic therapy
PE polyethylene; *or* pulmonary embolism; *or* pharyngo-oesophageal
PEG percutaneous endoscopic gastrostomy
PER persistent allergic rhinitis
PET polyethylene terephthalate; *or* positron emission tomography
PET-CT positron emission tomography/computed tomography
PET-MRI positron emission tomography-MRI
PF posterior fontanelle; *or* cisplatinum/5-fluorouracil

PF4 platelet factor 4
PFAPA periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis
PFS progression-free survival
PG paraganglioma
PGA polyglycolic acid
PGD2 prostaglandin D2
PGE1 prostaglandin-E1
PGI2 prostacycline; *or* prostaglandin I2
PGL persistent generalized lymphadenopathy
PHPT primary hyperparathyroidism
PI pulsatility index; *or* protease inhibitors
PI3K phosphotidyinositol 3
PICU paediatric intensive care unit
PIII parathyroid III
PIP peak inspiratory pressure
PIV parainfluenza virus; *or* parathyroid IV
PKA protein kinase A
PLAT paraganglioma-like adenoma of the thyroid
PLD potentially lethal damage
PM particulate matter
PNH paroxysmal nocturnal haemoglobinuria
PNIF peak nasal inspiratory flow
p.o. by mouth
POGO prescription of gain and output
POMC propiomelanocorticotrophin
PONV postoperative nausea/vomiting
PP pyrophosphate
PPD purified protein derivative; *or* parathyroid proliferative disease
PPV positive predictive value
PR3 proteinase 3
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRL polypeptide hormone prolactin
PRP platelet-rich plasma
PRPP 5-phospho-alpha-D-ribose 1-diphosphate
PSA prostate-specific antigen; *or* pleomorphic salivary adenoma; *or* persistent stapedial artery
PS-OCT polarization-sensitive OCT
PT prothrombin time
PTAH phosphotungstic acid haematoxylin
PTC papillary thyroid cancer; *or* psychophysical tuning curve
PTG parathyroid gland
PTH parathyroid hormone
PTHrP parathyroid hormone-related protein; *or* parathyroid hormone-related peptide
PTMC papillary thyroid microcarcinoma
pTNM pathological tumour, nodes, metastases
PTP post-transfusion purpura
PTU propylthiouracil
PUOF1 pituitary-specific positive transcription factor 1
PVA polyvinyl alcohol
PVC polyvinyl chloride
PW posterior wall

QALY quality adjusted life year
QOL quality of life

RA retinoic acid
RAE Ring, Adair, Elwyn
RAF rapidly accelerated fibrosarcoma signal-regulated kinase
RAI radioactive iodine
RANKL regulation of nuclear factor κB ligand
RANTES regulated on activation, normal T-cell expressed and secreted
RAS recurrent aphthous stomatitis; *or* rat sarcoma protein family
RAST radioallergosorbent test
RAT rapid antigen testing; *or* robotic-assisted thyroidectomy
RB retinoblastoma
RBC red blood cell
RCC Rathke cleft cyst; *or* red cell count
RCoA Royal College of Anaesthetists
RCT randomized controlled trial
RET rearranged during transfection
RF rheumatoid factor; *or* radio frequency
RFLP restriction fragment length polymorphism
RFRP RFamide-related peptide
RFTVR radiofrequency tissue volume reduction
rFVIIa recombinant factor VIIa
rhBMP-7 recombinant human bone morphogenetic protein 7
rhPTH recombinant human parathyroid hormone
rhTSH recombinant human TSH
RHD Reported Hearing Disability
RIG radiologically inserted gastrostomy
RLN recurrent laryngeal nerve
RLNP recurrent laryngeal nerve palsy
RNA ribonucleic acid
RNP ribonucleoprotein
ROS reactive oxygen species
ROSE rapid on-site evaluation
ROTEM thromboelastography
RP rapid prototyping; *or* relapsing polychondritis
RR relative risk

RRA radioiodine remnant ablation
RRR relative risk reduction
RSDI Rhinosinusitis Disability Index
RSOM rhinosinusitis outcome measure
RSTL relaxed skin tension line
RSV respiratory syncytial virus
RT radiotherapy
RTOG Radiation Therapy Oncology Group
rT3 reverse triiodothyronine
RTK receptor tyrosine kinase
RUDS reactive upper airways dysfunction syndrome

SA solitary adenoma; *or* situational awareness
SAD supraglottic airway device
SAGM saline-adenine-glucose-mannitol
SAPS simplified acute physiology score
SBS sick building syndrome
s.c. subcutaneous
SCC squamous cell carcinoma or cancer; *or* semicircular canal
SCCA squamous cell carcinoma antigen
SCCHN squamous cell carcinoma of the head and neck
SCID severe combined immunodeficiency
SCIT subcutaneous immunotherapy
SCL-90 Symptom Checklist-90
SCM sternocleidomastoid muscle
SCN severe congenital neutropenia; *or* solid cell nests
SEER Surveillance, Epidemiology, and End Results (program)
SERM selective-oestrogen receptor modifier
SETTLE spindle cell tumour with thymus-like differentiation
SF-36 Medical Outcome Study Short-Form 36-Item Health Survey
SFF speaking fundamental frequency; *or* solid free form fabrication
SHC SH2-containing protein
Shh sonic hedgehog
SHI syndromic hearing impairment
SHOT serious hazards of transfusion
SHPT secondary hyperparathyroidism
SIADH syndrome of inappropriate antidiuretic hormone
sIgE specific immunoglobulin E
SIGN Scottish Intercollegiate Guidelines Network
SIP sickness impact profile
siRNA small interfering ribonucleic acid
SLD sublethal damage
SLE systemic lupus erythematosus
SLICC Systemic Lupus International Collaborating Clinics
SLIT sublingual immunotherapy; *or* sublingually in drops or tablets
SLN superior laryngeal nerve
SMAS superficial or subcutaneous musculoaponeurotic system
SAMD submucosal diathermy
SMR submucosal resection
SMS short message service; *or* indium-111 pentetreotide
SNHL sensorineural hearing loss
SNOT sino-nasal outcome test
SNUC sinonasal undifferentiated carcinoma
SO2 sulphur dioxide
SOCS2 suppressors of cytokine signalling 2
SOE supraorbital ethmoid cells
SOFA sequential organ failure assessment
SOFT solitary oxyphil follicular tumour
SOS guanine nucleotide exchange factor (son of sevenless)
SPA sphenopalatine artery
SPECT single photon emission computed tomography
SPET single photon emission tomography
SPF sphenopalatine foramen
SPLINTS scrub practitioners list of intra-operative non-technical skills
SPT skin prick test; *or* station pull through
SPTX subtotal parathyroidectomy
SRS subacute rhinosinusitis
SS somatostatin
ssDNA single-stranded DNA
SSC superior semicircular canal; *or* Surviving Sepsis Campaign
SSEP steady-state potential
SSLP simple sequence length polymorphism
SSQ speech, spatial and qualities
SSTR1-5 somatostatin receptors 1-5
SSRI selective serotonin reuptake inhibitor
ST superior turbinate; *or* subtotal thyroidectomy
STAT signal transducer and activator of transcription
STD standard deviation
STRP short tandem repeat polymorphism
SUV standardized uptake value
SV stroke volume
SVCO superior vena caval obstruction
SVS selective venous sampling

SVCO superior vena cava obstruction
SVR systemic vascular resistance
Syk signal-propagating kinase

T thymine; *or* tumour
T1WI T1-weighted images
T2WI T2-weighted images
T3 triiodothyronine
T4 thyroxine
TAA tumour associated antigens
TACO transfusion-associated circulatory overload
TAD transfusion-associated dysponea
TAGVHD transfusion-associated graft-versus-host disease
TAM tumour associated macrophages
TB tuberculosis; *or Mycobacterium tuberculosis*
TBG thyroxine-binding globulin
TcT cytotoxic
^{99m}Tc technetium-99m
Tc-99m (v) DMSA pentavalent dimercaptosuccinic acid
TC thyroid cartilage
TCI target-controlled infusion
TCP tricalcium phosphate
TCR T-cell receptor
t.d.s. 3 times a day
TEG thromboelastography
TFT thyroid function test
TG thyroglobulin
TgAb thyroglobulin antibodies
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
Th1 T-helper 1 cell
Th2 T-helper 2 cell
THST thyroid hormone suppression therapy
THW thyroid hormone withdrawal
TI thyroid isthmusectomy
TIL tumour infiltrating lymphocytes
TIVA total intravenous anaesthesia
TKI tyrosine kinase inhibitor
TL total lobectomy
TME tumour microenvironment
TMC1 transmembrane channel-like gene 1
TMJ temporomandibular joint
TNF tumour necrosis factor
TNF-α tumour necrosis factor alpha
TNM tumour, node, metastasis
TNO transnasal oesophagosocpy
TOE transoesophageal echocardiography; *or Trichophyton*, *Oidiomycetes* and *Epidermophyton*
TOF tracheo-oesophageal fistula
TPO thyroid peroxidase; *or* thyroperoxidase
TPP thyrotoxic periodic paralysis
TPTX total parathyroidectomy
TPZ tirapazamine
TRALI transfusion-related acute lung injury
TRAM transverse rectus abdominis myocutaneous
TRH thyrotrophin-releasing hormone
tRNA transfer ribonucleic acid
TSA tumour specific antigens
TSH thyroid-stimulating hormone; *or* thyrotrophin
TSHoma TSH-secreting adenoma
TSH-R TSH receptor
TT thrombin time; *or* total thyroidectomy
TTF-1 thyroid transcription factor-1
TTP thrombotic thrombocytopeniac purpura
TUNEL TdT-mediated nick end labelling

U uracil
UCT unclassifiable complications of transfusion
UICC International Union Against Cancer
UIC urinary iodine concentration
UKRETS UK Registry of Endocrine and Thyroid Surgery
UMP uridine monophosphate
UNICEF United Nations Children's Fund
UP uncinate process
UPSIT University of Pennsylvania Smell Identification Test
URTI upper respiratory tract infection
US ultrasound; *or* ultrasonography
USH Usher syndrome
USH1B Usher syndrome type 1B
USS ultrasound scan
UV ultraviolet

V2R vasopressin type 2 receptor
VA Veterans' Affairs; *or* vestibular aqueduct
VAC vacuum-assisted closure
VAS visual analogue scale; *or* visual analogue score
VATS video-assisted thoracoscopic surgery
VC vocal cord

VCAM-1 vascular cell adhesion molecule-1
vCJD variant Creutzfeldt—Jakob disease
VCP vocal cord paralysis
VDA vascular disrupting agent
VEGF vascular endothelial growth factor
VEGFR vascular endothelial growth factor receptor
VF vocal fold
VHI Voice Handicap Index
VHI-10 Voice Handicap Index-10
VHQ Vertigo Handicap Questionnaire
VILI ventilator induced lung injury
VN vestibular nuclei; *or* vagus nerve
VNO vomero nasal organ
VOC volatile organic compound
VTE venous thromboembolism
VTFF vertex-to-floor
vWD von Willebrand disease
vWF von Willebrand factor
VZV varicella zoster virus

WBS whole-body scan
WDC-NOS well-differentiated carcinoma, not otherwise specified
WDTC well-differentiated thyroid cancer
WDT-UMP well-differentiated tumour of uncertain malignant potential
WHAFFT worrisome histologic alteration following fine-needle aspiration of the thyroid gland
WHO World Health Organization
WIFC widely invasive follicular carcinoma
WMD weighted mean difference
WP Woodruff's plexus
WPBA workplace based assessments
WS Waardenburg syndrome

XLA X-linked agammaglobulinaemia
XM crossmatch

YAC yeast artificial chromosome
YAG yttrium aluminium garnate

Section 1
Basic Sciences

CHAPTER 1

MOLECULAR BIOLOGY

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: 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%) 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) that 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 that detects mismatched DNA and efficient DNA repair pathways that 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% of it is non-coding, with all the genes being coded by the remaining 10% of the DNA. Within the non-coding 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 that determine when and in which cell types that gene is expressed, exons that are coding sequences and interspersed introns that are non-coding 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. However, these same genes can also be regulated by proteins that recognize methylated sequences called histones[2] and these in turn can be regulated by polycomb genes such as *BMI1*.[3] Transcription is the intra-nuclear 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.[4] Traditional dogma held that one gene produces one protein and therefore splicing was considered to occur simply in order to remove the non-coding 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.[5]

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 intra-cellular 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 that are principally involved in the respiratory chain. mtDNA is double-stranded but does not form a double-helix or chromosomes, but instead 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.

OTHER REGULATORS OF GENE EXPRESSION

In the last few years it has become apparent that gene expression is 'fine-tuned' by several classes of molecule. Small interfering RNAs (siRNAs) were first discovered in plants and are now widely used as research tools to suppress gene expression. However, natural versions of siRNAs exist (microRNAs- miRNAs) and are thought to be biologically significant regulators of gene expression.[6] miRNAs are small non-coding RNA molecules that function through base-pairing with mRNA, thus preventing their translation into proteins. There may be more than 1000 miRNAs in the human genome[7] and some of them are associated with oral cancer; they are also secreted into

body fluids making them candidates for the non-invasive detection of the disease.[8] In addition, long non-coding RNAs (ncRNAs) have been identified that are thought to regulate various aspects of gene expression, including transcription, splicing, translation, siRNA-directed gene regulation and epigenetic regulation.[9] Whilst the study of ncRNAs is still new they have been implicated in a number of diseases, including ageing and cancer.

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 non-coding sequences.
- Transcription is the intra-nuclear 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 T is replaced by U. 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 that 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.
- Gene expression can be modulated by naturally-occurring miRNAs and ncRNAs.

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 endonuclease acts *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 recognizes specific target sites based on sequences of four to eight nucleotides. As a specific, a 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.

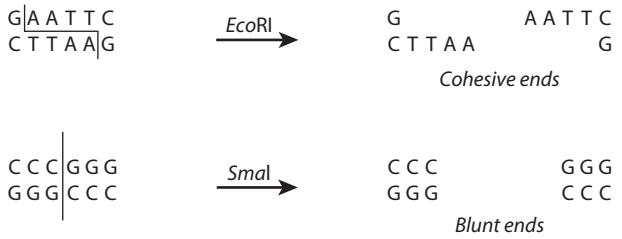

Figure 1.1 DNA cleavage by restriction endonucleases. Derived from Ref. 10, with permission.

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 towards the positive electrode with the smaller fragments travelling faster than the larger fragments.[10] The size of the fragment can be estimated by the use of a graduated DNA 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 that 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.

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 had thus begun. Cytogenetics is the study of chromosomal abnormalities and rearrangements. It currently has a major role to play in pre-natal diagnosis of Down 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 protooncogenes 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.[11]

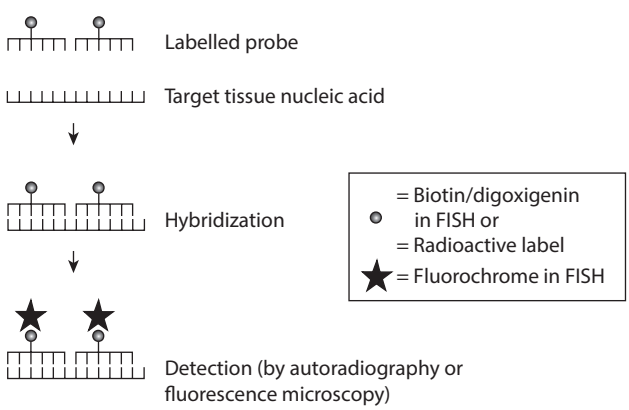

Figure 1.2 *In situ* hybridization.

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).[12] 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 that 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.[13] 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.[14] 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.

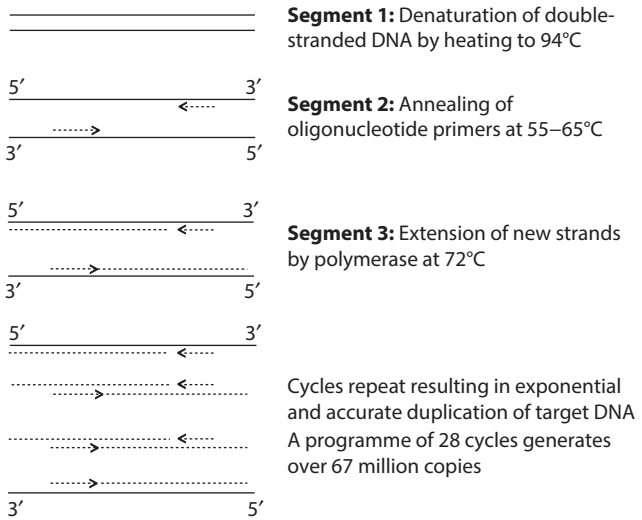

Figure 1.3 The polymerase chain reaction.

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 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.[15]

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. Down 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.[16] 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.[17] 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.[18] 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 non-coding DNA sequences, also referred to as simple sequence length polymorphisms (SSLP) or short tandem repeat 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

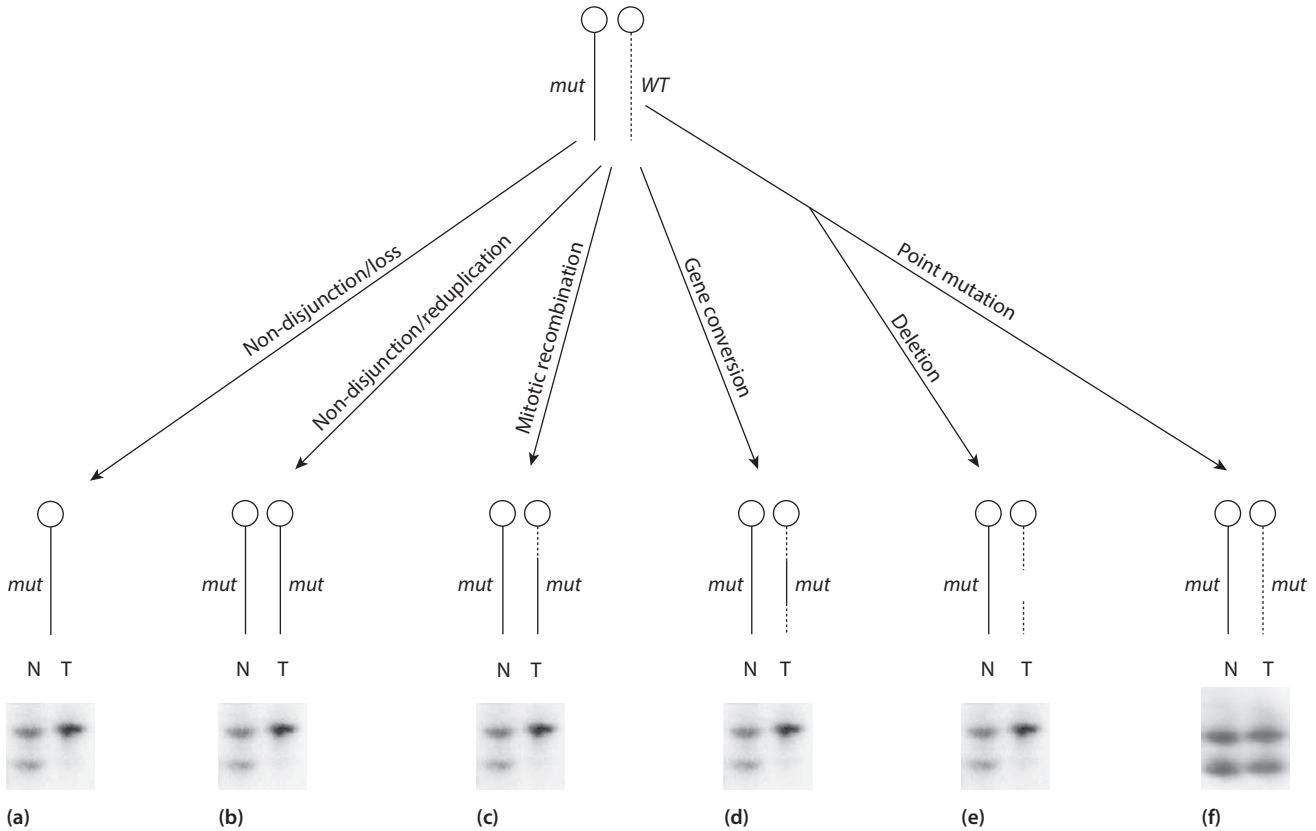

Figure 1.4 Chromosomal mechanisms that could reveal recessive mutations. In this example, before cell division, the tissue concerned carries a mutation in one copy of the hypothetical tumour suppressor gene. In each of the scenarios **(a–f)**, the recessive mutation is revealed. If the individual is 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 that escapes observed loss of heterozygosity is F. *mut*, mutated; N, normal; T, tumour; *WT*, wildtype. After Ref. 17, with permission.

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 non-informative 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.[19] 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, 17p13, 13q14, 4p, 5q21 and several discrete regions on 3p and 8p.[20, 21]

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' that dramatically alters the coding downstream from the mutation. Base substitution is a more common form of mutation in coding DNA, which may have a range of consequences on the function of the gene; a loss of function (e.g. *p53*, *Rb*), a gain in function, often due to stabilization of the active protein (e.g. *c-erbB2*, *K-ras*) or no net functional effect. Since an amino acid may be encoded by different codons with a 'third base wobble' (e.g. GU**A**, GA**C**, GU**G** and GU**U** all encode valine), a substitution of the third base would result in no change to the amino acid. This is known as a silent substitution. At the other extreme is the nonsense mutation, whereby base substitution results in a stop codon which leads to truncation of the polypeptide and a dramatic reduction in function.

Loss of function in the presence of a normal (wildtype) allele may occur as a result of transcription silencing. The methylation status of CpG islands surrounding the promoter regions of genes determines whether a particular gene is expressed within a cell such that methylation of a CpG island 'switches off' the gene that it is regulating. CpG islands regulating housekeeping genes (i.e. genes encoding proteins essential for cell survival) are unmethylated in all cell types whereas those regulating cell-specific genes (e.g. muscle-specific actin gene in muscle cells), are only unmethylated in the relevant cell. Many tumour suppressor genes (e.g. *CDKN2A (*p16^{INK4A}*)*, *APC*, *RASSF1A*) are now recognized to be inactivated by hypermethylation of the promoter region in malignant tumours.

Gene sequencing

Recently a variety of next generation sequencing methods have been applied to the field. One method is to construct a library of DNA fragments and to use biotinylated RNA baits to capture the exomic sequences using streptavidin coated magnetic beads prior to loading them onto the sequencing machine following digestion of the RNA bait and a few cycles of PCR. This strategy was able to obtain 10 or more sequencing reads for over 90% of the targeted bases and this approach and similar strategies have revealed the mutational landscape of head and neck squamous cell carcinoma, including the frequent mutation of the *NOTCH1* gene, which had not been identified previously.[22–24]

Proteomics and metabolomics

As the Human Genome Mapping Project powers its way towards a high-resolution sequence of the entire genome, the natural progression of research has been towards the elucidation of the repertoire of proteins that control cell signalling and cell growth. Proteomics is the profiling of proteins in cells and serum by two-dimensional gel analysis separating proteins by charge and mass, by X-ray crystallography and by mass spectrometry.[25] Proteomics has the ability to identify post-translational modifications, some of which are cancer cell-specific, which would not be detected by genetic or expression profiling. The power of this approach is particularly evident in cancer studies as it has the ability to compare the entire protein pattern of tumour tissue and normal tissue in a manner analogous to comparative genomic hybridization.

However, the functional consequences of changes to the proteome, especially some enzymes, can only be inferred and a more direct approach is to measure the levels of small molecules, or metabolites. Metabolomics is the global analysis of metabolites but is a relatively new discipline and no single technique is suitable for the analysis of all different types of molecule. Therefore, a mixture of techniques such as gas chromatography, high-pressure liquid chromatography and capillary electrophoresis are used to separate metabolites and the molecules are then identified using methods such as mass spectrometry. Metabolomics has already been applied to the detection of oral cancer in saliva[26] and serum.[27]

Telomerase

Aberration of telomere biology has a now well-recognized role to play in cancer development. The length of the telomere is maintained in germline cells by the enzyme telomerase that is absent in normal somatic cells.[28] This observation led to the theory that progressive shortening

of telomeres with each cell division leads to cell senescence and ageing of the organism. Several mechanisms for this have been proposed. A critical shortening of the telomere may leave a non-telomere-free DNA end that signals cell cycle arrest. Telomere loss could also extend to the deletion or inactivation of genes located subtelomerically, again leading to cell cycle arrest. Two important consequences of critical telomere shortening in cells that survive the cell crisis are genomic rearrangements and chromosomal loss, which may in turn lead to malignant transformation. This is particularly relevant to rapidly dividing and regenerating tissues, such as skin and mucosa. Paradoxically, while some of these survivors will subsequently go into cell cycle arrest due to critical telomere length shortening, a proportion will then express telomerase activity. Such activity is capable of cell immortalization by maintaining telomere length indefinitely and its role in cancer is now unquestionable. Telomerase activity has been demonstrated in 80% of oral cancers and around 50% of oral leukoplakia lesions.[29] Even among premalignant lesions, telomerase activity was associated with degree of dysplasia, suggesting that telomerase activation occurs during the late stage of oral premalignancy. The potential for anti-telomerase drugs as a novel treatment remains promising, especially as they are now thought to target cancer stem cells.[30]

KEY POINTS

- Practical techniques based on loss of heterozygosity of tumour DNA are based on Knudson's two-hit hypothesis, which states that two genetic events are required to inactivate the gene that prevents the development of a condition.
- The number of microsatellite repeats (i.e. non-coding base pairs dispersed throughout the genome) may differ between two alleles in the same person making that person heterozygous for that particular allele. If tumour DNA from such a subject when amplified by PCR yields only one product, the tumour is said to show loss of heterozygosity implying allelic loss.
- Inactivation of genes can occur by:
  - allelic deletion
  - genetic mutation
  - transcriptional silencing
  - conversion of protooncogene to oncogene due to gene amplification.
- Some mutations do not result in change of function. They can be silent or nonsense mutations.
- Next generation sequencing has produced a mutational landscape of head and neck cancer.
- Proteomics refers to the profiling of proteins in cells and serum by 2D gel analysis, X-ray crystallography and by examination of protein interactions. This can be used to identify post-translational modifications, some of which are cancer cell specific and are not detected by genetic profiling.
- Metabolomics can be used to detect small molecules accumulating in the tissues and body fluids of oral cancer patients.
- Critical telomere shortening or inefficient telomere DNA repair can lead to both cell cycle arrest and cell immortalization due to expression of telomerase, which, for example, has been demonstrated in 80% of oral cancers.

MAPPING AND IDENTIFICATION OF GENES ASSOCIATED WITH DISEASE

The traditional approach to understanding the molecular biology of disease was to look for and characterize the abnormal protein. Diabetes mellitus and sickle cell anaemia are two conditions that were elucidated at the molecular level in this way. Finding the protein when present in minute quantities, in an inaccessible site such as the inner ear, or when nothing is known of its mode of action, is, however, virtually impossible. This is the case with most of the genes involved in cellular growth control and also in inner ear function. Our approach to understanding such conditions relies on determining the chromosomal location, isolating and sequencing the gene so that the structure of the protein can be determined. This is known as the reverse genetic or positional cloning technique.

Strategies employed in determining the sites of these disease genes include cytogenetic analysis, molecular genetic analysis (typically LOH studies) and linkage analysis. Where a clearcut inheritance of a disease can be demonstrated, then linkage analysis can be useful in determining the location of the responsible gene. The key advance that has made this approach increasingly successful has been the construction of a high-resolution linkage map of the entire human genome. This map consists of genetic markers spaced less than 1 centimorgan apart and the process of linkage involves determining which of these the disease gene is close to. Analysis of the coinheritance of the genetic marker and the disease trait in families allows one to determine the probability of their physical proximity or linkage to each other. The statistical probability of linkage is expressed in terms of LOD scores. LOD is short for logarithm to the base 10 of the odds that the markers are linked at a recombination distance of N centimorgans. An LOD score of 3.0 favours linkage while a score of –2.0 effectively rules out linkage.

Successful linkage analysis typically requires large pedigrees with many individuals known to have the disease trait and likewise many confirmed to be free of the disease. The process involves initial family analysis with clinical evaluation and accurate diagnosis. DNA samples are then obtained from each individual and genotyping and linkage analysis can then be carried out. Linkage and molecular deletion analysis generate genetic markers either side of the disease gene location. These genetic markers can be used to identify 'chunks of genomic DNA' cloned into yeast (yeast artificial chromosomes (YAC)) or bacteria (bacterial artificial chromosomes/P1 artificial chromosomes (BAC/PAC)) and organized into libraries. By a number of methods, these 'chunks' of genomic DNA can be directionally organized to produce a physical map of the region of interest from which candidate disease genes can be identified. The Human Genome Mapping Project has, to a great extent, physically mapped the human genome such that in some cases, when the region of interest is sufficiently small, all genes known to be between the markers can be considered positional candidates. The candidates are then analysed in disease

families until one is found that demonstrates mutations in affected individuals.

To facilitate the identification of the disease gene from a number of candidates within a particular region, several strategies are available. One such approach exploits our knowledge of animal models of the diseases that parallel human inherited disorders. Another potential source of candidate genes is to identify and characterize genes that are expressed within a particular tissue. Genes expressed within the cochlea, for example, represent the genes critical for cochlear function and thus are excellent candidate genes for hereditary hearing loss.

FUTURE RESEARCH

Although giant strides have already been made in the delineation of molecular events underlying disease processes, the knowledge of these events is far from comprehensive. A clearly identifiable adenoma–carcinoma sequence facilitated the correlation between genetic and histopathological progression models in colorectal cancer.[19] Several similar progression models have been proposed in head and neck squamous cell carcinoma evolution from epithelial dysplasia through to frank carcinoma, but the heterogeneity of carcinomas in different subsites precludes a molecular genetic progression model of equal rigour to that in colorectal cancer. Nevertheless, *p16* and *p53* inactivation have been identified as the two most frequent and critical events in head and neck carcinogenesis. An understanding of the sequence of genetic aberrations that occur in pathogenesis of tumours can assist in the prediction of progression from premalignant conditions to frank malignancy. An example of this is seen in the accumulation of genetic abnormalities in oral epithelium leading to the progression of oral dysplasia to oral squamous cell carcinoma. By analysing for loss of heterozygosity at 19 microsatellite loci in a series of oral dysplastic lesions and oral malignancies, Rosin et al.[31] showed that LOH at 3p and/or 9p occurred in virtually all cases of oral dysplasia which progressed to frank malignancy implying a 'gatekeeper' role of genes at those loci in the development of oral cancer, in themselves imparting a 3.8-fold increased relative risk of progression to squamous carcinoma. Furthermore, additional LOH at 4q, 8p, 11q or 17p imparted a 33-fold increased relative risk for developing cancer.[31] In certain cases, molecular genetic profiling has added a new dimension to age-old debates. For example, discordant genetic anomalies in inverted sinonasal papillomas and sinonasal carcinomas lend weight to the opinion that the former does not undergo malignant degeneration into the latter.[32]

Traditional methods of allelotyping and mutational analysis remain extremely time-consuming and labour-intensive. Recent years have seen the development of gene arrays (or 'gene chips') that allow the rapid assessment of the genetic profile of tumours or cell lines.[33] cDNA of up to 30 000 genes can be placed in arrays on glass slides on to which DNA and RNA samples can be allowed to hybridize using an automated two-colour fluorescence method for detection.[34] Hybridization with DNA can yield extensive genomic information, while hybridization with RNA takes genetic profiling a step further by semiquantitatively analysing the expression of genes rather than simply the presence or absence of the DNA. As the genetic aberrations and pathways associated with specific tumour development become better dissected, 'designer' chips can be produced that allow for screening for known mutations of those involved genes.[35] Array technology has also been married with molecular cytogenetics to produce array-based comparative genomic hybridization, which obviates the need for metaphase chromosome spreads for CGH.

The clinician might be forgiven for an expression of cynicism regarding the 'molecular revolution', feeling that little has changed despite ambitious predictions. The translation of molecular biology research into clinical practice – 'from laboratory to bedside' – is without doubt the greatest challenge facing the clinician scientist. Progress so far has been largely at the level of disease classification, premorbid diagnosis and patient counselling. However, several discrete arms to translational research have hinted at the future role of genetic analysis determining the likely effectiveness of existing anti-cancer treatments. There are also isolated examples of effective novel therapeutic interventions.

Molecular analysis played a vital role in differentiating neurofibromatosis type I from neurofibromatosis type II, and it now seems difficult to understand how we ever confused the two in the first place. Such clarity of diagnosis is also anticipated for many syndromic and non-syndromic causes of sensorineural hearing loss as the genes are characterized and the clinical features analysed in more detail. This may enable clinicians to determine in which cases hearing loss will be progressive and target monitoring more appropriately. Diagnostic genetic testing will also become increasingly available to families with hereditary hearing loss and clinicians will need to be conversant with the ethical issues of testing and the implications of the results. By characterizing hearing loss at the molecular level we are also developing a greater understanding of inner ear physiology as the critical proteins involved in hearing become elucidated. This may lead to the development of agents able to repair and regenerate the diseased inner ear. The administration of these agents is already being evaluated using miniature infusion pumps.

It is hoped that in the future molecular characterization of tumour tissue will provide for a more accurate diagnosis and prognosis than conventional histopathological analysis. This may lead to a more rational treatment plan based on molecular features. Some genotype–phenotype correlations have already been made, particularly with respect to radio- and chemoresistance in tumours, but confirmation is needed with larger sample sizes as to their applicability into clinical practice. Refinement of the staging of tumours by probing of resection margins and the detection of histological subclinical metastatic disease in regional lymph nodes have been elegantly demonstrated by Brennan et al.[36] at Johns Hopkins. However, the technical complexity of the methodology has precluded its widespread application in the clinical arena. The development of technically simpler but equally sensitive techniques will inevitably render molecular staging routine in oncological practice. Although surveillance for tumour recurrence is less of a problem in the upper aerodigestive tract when compared with intra-abdominal malignancies, the emergence of molecular markers in saliva and serum will have a role in follow-up protocols for head and neck cancers.[37]

A comprehensive understanding of the molecular mechanisms underlying disease processes gives the potential of therapeutic restoration of DNA or protein function, as well as exploitation of the genetic abnormality for targeting of therapy. An example of the latter is the use of ONYX-015. ONYX-015 is an E1B 55-kDa gene-deleted adenovirus engineered to selectively replicate in and lyse *p53*-deficient cells while sparing normal cells. This tumour-targeting property has led

to a successful phase II trial of concomitant ONYX-015 and cisplatin/5-FU in the treatment of recurrent HNSCC, which indicated substantial objective responses as well as a high proportion of complete responses.[38] Post-treatment biopsies of tumour masses confirmed the replication selectivity of the virus *in vivo*.

A consideration of some of the landmarks in molecular biology (e.g. enzymatic DNA cleavage (1970) and PCR (1987)) readily indicates that molecular biology is a relatively young science. However, the rapid development of molecular techniques of such power and diversity as comparative genomic hybridization and gene array technology has permitted the dissection of molecular pathways and the identification of their disruption in disease processes. Some of these processes in specific diseases will be discussed in subsequent chapters. The future in the laboratory lies in the extension of our understanding of these molecular processes and the future in the clinic lies in the exploitation of these molecular techniques in better informing disease classification, staging and treatment:

- Development of a molecular genetic progression model for head and neck squamous cell carcinoma of similar rigour to that for colorectal carcinoma.
- Development of gene arrays or gene chips that allow the rapid assessment of the genetic profile of tumours and can allow semiquantitative analysis of gene expression.
- Designer chips may be produced that allow for screening for unknown mutations of involved genes.
- Potential role for genetic analysis in determining the likely effectiveness of existing anti-cancer treatments.
- Providing more accurate diagnosis and prognosis than conventional histopathological techniques.
- Potential therapeutic restoration of DNA or protein function, as well as exploitation of a genetic abnormality for targeting therapy (e.g. use of ONYX-015).

KEY POINTS

- Strategies employed in determining the sites of disease genes that code for the abnormal proteins include cytogenetic, molecular genetic and linkage analysis.
- Whilst genomics and other omics has generated a large body of data, cancers are complicated tissues. Future research may shift towards understanding the cancer environment and how perhaps to target this in future therapeutic strategies.

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CHAPTER 2

GENETICS IN OTOLOGY AND NEUROTOLOGY

Mohammed-Iqbal Syed

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using a variety of relevant generic keywords, including: DNA, genetics, hereditary hearing loss, connexin 26, neurofibromatosis 2 and familial paragangliomas.

INTRODUCTION

Advances in molecular genetics have helped to identify causative genes and proteins responsible for pathologies; this knowledge is pertinent to molecular target therapy and promises novel therapeutic interventions.

This chapter aims to review the mechanisms and principles of molecular genetics of hearing impairment, vestibular schwannoma, and glomus tumours, and will keep the reader abreast of new developments that may be relevant to identifying and treating these diseases in clinical practice.

MOLECULAR GENETICS OF HEARING LOSS

Hearing loss is the most frequent sensory impairment in humans, with significant social and psychological implications. Permanent childhood hearing impairment of a moderate or greater degree (i.e. detection thresholds 40 decibels hearing level averaged across 0.5, 1, 2 and 4 kHz) is present at birth in about 1.6 per 1000 live births, of which approximately 1.0 in 1000 are bilateral impairments and 0.6 in 1000 are unilateral impairments.[1, 2] However, studies have shown that the prevalence of permanent childhood hearing impairment continues to increase through infancy, and by the school entry hearing screen (4–5 years of age) possibly affects 3.5 per 1000 children.[2] It is estimated that at least two thirds of cases of childhood-onset hearing loss have a genetic cause, with the remaining third caused by environmental factors (e.g. cytomegalovirus infection, meningitis, acquired conductive loss, and the impact of extracorporeal membrane oxygenation (ECMO)).[3] Improved clinical knowledge, awareness, and advances in antibiotics and vaccines has led to a decline in hearing loss resulting from environmental factors. Likewise, significant progress in the genetics of hereditary hearing impairment (HHI) has improved our understanding of the causes and early detection of HHI.

Classification

The most useful distinction in hereditary hearing impairment (HHI) is syndromic versus non-syndromic. When SNHL occurs in isolation it is termed non-syndromic and when it is accompanied by other systemic disturbances it is termed syndromic. The majority of hearing impairments are non-syndromic (~70%), whereas a minority are syndromic (~30%).

Non-syndromic HHI is further classified by mode of inheritance:

- Autosomal recessive ~80%
- Autosomal dominant ~18%.[4]

Rare modes of transmission include X-linked and mitochondrial transmission, which account for the remaining 2% of hearing impairment.