
Contents

1Development of the Lung	1
1.1Development of the Lung.	1
1.2Genetic Control of the Development.	4
1.3Comparison of Lung Development Across Species.	5
References.	6
2Normal Lung	7
2.1Normal Lung.	7
2.2Gross Morphology.	7
2.3The Airways.	9
2.4Comparison of Human Lung to Other Species.	16
References.	18
3Pediatric Pulmonary Pathology	21
3.1Developmental and Inherited Lung Diseases.	21
3.2Aplasia and Acinar/Alveolar Dysgenesis.	21
3.3Tracheal Agenesis.	24
3.4Growth Retardation.	24
3.5Bronchial Atresia, Stenosis, and Bronchomalacia.	25
3.6Vascular Malformations.	25
3.6.1Alveolar Capillary Dysplasia With/Without Misalignment of Pulmonary Veins.	25
3.6.2TBX4-Related Pulmonary Hypertension and Malformation.	26
3.6.3Diffuse and Localized AV Anastomoses.	27
3.6.4Ehlers–Danlos Syndrome Type IV.	28
3.6.5Veno-Occlusive Disease.	28
3.6.6Anomalous Systemic Arterial Supply, Including Sequestration.	29
3.7Malformations of the Airway System.	30
3.7.1Congenital Pulmonary Airway Malformation (CPAM, Formerly CCAM) Type 1, 2, 3.	30
3.7.2Bronchogenic Cyst.	35
3.7.3Congenital Lobar Emphysema.	36
3.7.4Williams–Campbell Syndrome.	36
3.7.5Mounier–Kuhn Syndrome.	37
3.7.6Birt–Hogg–Dubé (BHD) Syndrome.	38

Immotile Cilia Syndrome.....	38
LungPathologyinChromosomalAbnormalities	39
Inborn Errors of Metabolism. 41	
Pulmonary Interstitial Glycogenosis	41
Niemann–PickSyndrome	41
PulmonaryInvolvementinGaucherDisease	42
Surfactant-RelatedDisorders . 43	
Cystic Fibrosis	45
NeuroendocrineCellHyperplasiaofInfancy(NEHI)	46
Pneumonia in Childhood Including Noninfectious	
Interstitial Pneumonias	47
ChronicPneumoniaofInfancy(CPI) 47	
Non-SpecificInterstitialPneumonia(NSIP)	48
LymphocyticInterstitialPneumonia(LIP)	48
COPASyndrome..... 48	
Idiopathic Eosinophilic Pneumonia in Children	49
Bronchopulmonary Dysplasia (BPD)	49
Mendelson Syndrome in	
Children and Silent	
NocturnalAspiration..... 50	
References	51
4 Edema.....	59
Edema	59
High-Altitude Pulmonary Edema (HAPE)	59
Inflammation-AssociatedEdema	61
References	62
5 Air Filling Diseases.....	63
Atelectasis	63
Emphysema..... 63	
Emphysema and Lung Function	69
FactorsContributingtoEmphysemaDevelopment	70
References	72
6 AirwayDiseases	75
Tracheitis,Bronchitis	75
BronchialAsthma	77
Bronchiolitis..... 81	
References	94
7 Smoking-RelatedLung Diseases	97
Langerhans Cell Histiocytosis	97
Respiratory Bronchiolitis: Interstitial Lung Disease	
(RBILD)	100
DesquamativeInterstitialPneumonia(DIP)	102
Smoking-	
InducedInterstitialFibro	
sis(SRIF)/RespiratoryB	
ronchiolitis-Associated	
Interstitial Lung	
Disease	
(RBILD)	103

Chronic Obstructive Pulmonary Disease (COPD)	104
What Are the Mechanisms? Why Not Every Smoker Develops COPD?	105
But What Are the Reasons for these Lymphocytic Infiltrations?	107
Acute Lung Injury and Other Morphological Changes Due to Cigarette Smoke Inhalation	107
Effects of Shisha Smoking	108
References	108
8 Pneumonia	113
Alveolar Pneumonias (Lobar and Bronchopneumonia)	113
Alveolar Pneumonias (Bronchopneumonia, Lobar Pneumonia; Adult and Childhood)	115
Diffuse Alveolar Damage (DAD), Acute Interstitial Pneumonia	117
Lymphocytic Interstitial Pneumonia (LIP)	121
Giant Cell Interstitial Pneumonia (GIP; See Also Under Pneumoconiosis)	124
The Infectious Organisms	124
HIV Infection and the Lung	129
SARS-CoV2 Infection	129
Pneumonia in Children	131
Granulomatous Pneumonias	136
Introduction	136
What Influences Granuloma Formation?	136
Why Necrosis?	136
Morphologic Spectrum of Epithelioid Cell Granulomas	138
The Causes of Epithelioid Cell Granulomas and Their Differential Diagnosis	139
Infectious Epithelioid Cell Granulomas	139
The Noninfectious Epithelioid Cell Granuloma	151
Fibrosing Pneumonias (Interstitial Pneumonias)	166
Historical Remarks on Interstitial Pneumonia Classification	166
Usual Interstitial Pneumonia (UIP)/Idiopathic Pulmonary Fibrosis (IPF)	167
Familial IPF (FIPF)	178
Non-specific Interstitial Pneumonia (NSIP)	179
Organizing and Cryptogenic Organizing Pneumonia (OP, COP)	181
Airway-Centered Interstitial Fibrosis (ACIF)	183
Smoking-Related Interstitial Fibrosis (SRIF)	184
Radiation-Induced Fibrosis	184
Atypical Pulmonary Fibrosis	184
End-Stage Fibrosis	185
References	186

9 Lung Diseases Based on Adverse Immune Reactions.....	195
Introduction into Interstitial Lung Diseases	195
Autoimmune Diseases	195
Rheumatoid Lung Disease.....	195
Systemic Lupus Erythematoses.....	200
Systemic Sclerosis	203
Dermatomyositis/Polyserositis	206
Sjögren's Disease	208
Mixed Collagen Vascular Diseases (CVD)	210
Goodpasture Syndrome	211
Other Autoimmune Diseases Affecting the Lung.....	213
IgG4-Related Sclerosis	214
Phospholipid Autoantibody- Mediated Lung Disease	214
Surfactant-Related Interstitial Pneumonias:	
Alveolar Proteinosis	215
Autoimmune Diseases in Childhood	216
Diseases of the Innate Immune System Based on Genetic Abnormalities	216
Idiopathic Pulmonary Hemosiderosis	216
Lymphangioleiomyomatosis (LAM).....	218
Hermansky-Pudlak Syndrome	218
Erdheim-Chester Disease.....	220
Allergic Diseases	220
Chronic and Subacute Hypersensitivity	
Pneumonia	220
Allergic Bronchopulmonary Mycosis.....	221
Drug Allergy	223
References	227
10 Eosinophilic Lung Diseases.....	231
Introduction	231
Allergic or Hyperreactive Diseases	231
Allergic Bronchopulmonary Mycosis	
(Aspergillosis)	231
Eosinophilic Pneumonias (EP).....	234
Acute Eosinophilic Pneumonia	235
Chronic Eosinophilic Pneumonia	240
References	241
11 Vascular Lung Diseases.....	243
Infarct and Thromboembolic Disease.....	243
Vasculitis	243
Classification of Vasculitis.....	243
Granulomatosis with Polyangiitis	245
Eosinophilic Granulomatosis with Polyangiitis (EGPA, Formerly Called Churg-Strauss Vasculitis, CSS)	248

Microscopicpolyangiitis	249
PanarteritisNodosaa	252
SecondaryVasculitiswithInfection	253
SecondaryVasculitisWithoutInfection	254
VascularDiseasesandMalformation	255
Malformation and Systemic (Inborn)Vascular DiseasesinChildren.....	256
Pulmonary Hypertension	256
Mechanisms of PAH.....	263
AlveolarHemorrhage	263
DiseasesoftheLymphatics(Adultand Childhood).....	264
Malformation	264
Obstruction.....	265
Inflammation.....	265
References	265
12 MetabolicLungDiseases	269
Amyloidosis	269
Disturbed Calcium Metabolism.....	271
CalcificationandOsseousMetaplasia	271
Metabolic/Metastatic Pulmonary Calcification.....	273
Microlithiasis	273
LipidandSurfactant Metabolism.....	275
AlveolarProteinosis.....	275
LipidAccumulationSyndromes	277
Glycogen Storage Disease.....	280
Idiopathic Pulmonary Hemosiderosis.....	281
References	282
13 EnvironmentallyInducedLungDiseases andPneumoconiosis	285
Introduction	285
Silicosis	287
Silicatosis	290
Asbestosis	290
Other Silicatoses	295
Metal-Induced Pneumoconiosis and Disease	297
Hard Metal Lung Disease	298
Aluminosis	298
Chromium andVanadium.....	298
Tungsten	300
Cobalt and Cadmium	300
Mercury.....	304
Nickel.....	304
Arsenic	304
Indium,Tin,Iron.....	305
RareMetals and ChronicAllergic Metal Diseases	305

CottonDust,FlockWorkersLung,Byssinosis	308
Man-Made Fibers, Hydrocarbon Compounds, and Polyvinyls	308
Nanoparticles.....	308
Pesticides and Insecticides	309
Inhalation of Combustibles.....	310
Cocaine,Marijuana	311
MedicalDevices	311
References	312
14 IatrogenicLungPathology	319
Drug-Induced Interstitial Lung Diseases.....	319
ActionofDrugsandMorphologicChanges	
AssociatedwithDrug Metabolism	319
GranulomatousReactions	321
DADPattern.....	321
OrganizingPneumoniaPattern	322
NSIPandLIP Patterns	322
UIPPattern.....	323
Vasculitis.....	324
Edema	324
Fibrinous Pneumonia	324
Lipid Pneumonia.....	327
IatrogenicPathologyby Radiation	327
References	328
15 BronchoalveolarLavageas a DiagnosticandResearchTool.....	331
WhereandWhen Doing BAL?	331
ProcessingBAL.....	333
References	334
16 LungTransplantation-RelatedPathology	335
Fiorella Calabrese	
16.1 ExplantPathology.....	335
16.1.1ObstructiveDiseases.....	335
16.1.2Emphysema.....	336
16.1.3Restrictive Diseases.....	336
16.1.4VascularDisease(PulmonaryHypertension)....	338
16.2 PerioperativeComplications.....	338
16.3 LungAllograft Rejection.....	339
16.3.1Hyperacute Lung Rejection.....	339
16.3.2AcuteRejection (GradeA).....	339
16.3.3ChronicRejection (Grade C and D).....	339
16.3.4Emerging Immunological Lesions	342
16.3.5Chronic LungAllograft Dysfunction— CLAD—(RestrictiveAllograftSyndrome-RAS)...	343
16.4 Infections	344
16.4.1ViralInfection.....	345
16.4.2BacterialInfection.....	345
16.4.3FungalInfections.....	345

Tumors	346
Other Complications.....	347
References.....	347
17 LungTumors.....	353
EpithelialTumors.....	353
Benign EpithelialTumors.....	353
Bronchial MucousGlandAdenoma (SalivaryGlandTypeAdenoma)	353
Mucous GlandAdenoma.....	354
Serous and Mucinous Cystadenoma,Including BorderlineVariants.....	355
Cystadenofibroma.....	356
PleomorphicAdenoma	358
Myoepithelioma.....	359
PapillomainAdultandChildhood	360
PapillaryAdenoma	366
BiphasicPapillaryAdenoma and Myomatous Hamartoma	368
Ciliated MuconodularTumor (CMPT)	369
Sclerosing Pneumocytoma (FormerlySclerosing Hemangioma).....	369
AlveolarAdenoma (Pneumocytoma)	375
Multifocal NodularPneumocyte Hyperplasia (MNPH)	377
Endometriosis	379
IntrapulmonaryThymoma.....	379
In Situ Carcinoma and Precursor Lesions.....	382
Squamous Cell Dysplasia or Intraepithelial Neoplasia.....	383
AtypicalAdenomatous Hyperplasia	385
BronchiolarColumnar Cell Dysplasia	386
Atypical Goblet Cell Hyperplasia.....	388
Neuroendocrine Cell Hyperplasia.....	390
Malignant EpithelialTumors	393
Common Carcinomas	402
Lymphoepithelioma-likeCarcinoma.....	435
AdenosquamousCarcinoma	435
NeuroendocrineCarcinomas	438
SalivaryGlandTypeCarcinomas.....	459
The Sarcomatoid Carcinomas.....	466
RareUndifferentiatedCarcinomas	475
Primary Intrapulmonary Germ Cell Neoplasms	477
BenignandMalignant MesenchymalTumors	478
Hamartoma.....	479
Smooth MuscleTumors.....	481

Leiomyoma.....	481
Leiomyosarcoma and MetastasizingLeiomyoma.....	482
Lymphangioleiomyomatosis(LAM)	484
PEComa(ClearCellTumor,SugarTumor).....	489
FibromatousTumors	492
IntrapulmonarySolitaryFibrous Tumor (Fibroma), Benign and Malignant.....	492
InflammatoryPseudotumor(IPT)/I nflammatory Myofibroblastic Tumor(IMT)	494
IGG4-RelatedFibrosis/Tumor	497
Undifferentiated Soft TissueSarcoma(FormerlyMali gnantFibrous Histiocytoma, Also Epithelioid Sarcoma)	499
Chondroma, Osteoma, Lipoma	504
TumorswithNervousDifferentiation	506
Schwannoma and MalignantPeripheralNerveShe etTumor(MNPST) Granular Cell Schwannoma,MyxoidSchwannoma.....	506
TritonTumor.....	511
Paraganglioma	511
Pulmonary Meningioma.....	513
VascularTumors.....	514
Hemangioma.....	514
Pulmonary Capillary Hemangiomatosis	516
Epithelioid Hemangiendothelioma,Angiosarcoma... Pulmonary Artery Intimal Sarcoma(PAIS;GiantCellSarcoma of LargePulmonaryBloodVessels;Vasc ularLeiomyosarcoma of Large Pulmonary BloodVessels)	518
Kaposi Sarcoma.....	527
Lymphangioma, Lymphangiomatosis(Pulmonary and Systemic)	528
Lymphangiosarcoma.....	531
Meningothelial Nodules (Chemodectoma).....	532
TumorsofPericyticLineage	534
Primary Melanoma of the Bronchus	539
HematologicTumorsPrimarilyArisingintheLung.....	540
Pseudolymphoma	540
PosttransplantLymphoproliferativeDisease.....	540
Lymphomas.....	541

Extranodal Marginal Zone Lymphoma of BALT Type (BALT-Lymphoma)	541
Chronic Lymphocytic Leukemia (CLL)	542
Lymphoplasmacytic Lymphoma	542
Diffuse Large B-cell Lymphoma	543
Lymphomatoid Granulomatosis	545
Castleman's and Waldenstrom's Disease	545
Dendritic Cell and Histiocytic Tumors	551
Interdigitating and Follicular Dendritic (Reticulum) Cell Tumor	551
Malignant Langerhans Cell Histiocytosis (Abt-Letterer-Siwe)	551
Malignant Histiocytic Sarcoma	551
Erdheim-Chester Disease	555
Childhood Tumors	558
Congenital Peribronchial Myofibroblastic Tumor	558
Fetal Lung Interstitial Tumor (FLIT)	558
Pleuropulmonary Blastoma	560
Adenocarcinoma of the Lung Arising in CPAM	564
Squamous Cell Papilloma and Papillomatosis	565
Capillary Hemangioma	565
References	565
18 Metastasis	597
Tumor Establishment and Cell Migration	597
Angiogenesis, Hypoxia, and Stroma (Microenvironment)	597
The Role of Hypoxia in Tumor Cell Migration and Metastasis	599
Escaping Immune Cell Attack	601
Migration	603
Vascular Invasion, Lymphatic/Hematologic	607
Blood Vessels	607
Lymphatic Vessels	608
Extravasation	608
Preparing the Distant Metastatic Focus	609
Angiogenesis	610
Metastasis	610
Brain Metastasis	612
Lung Metastasis	614
Bone Metastasis	614
Pleural Metastasis	615
Lymph Node Metastasis	615
Metastasis to the Lung	617
Differentiation of Metastasis from Primary Lung Carcinomas	617

Examples of Common Carcinoma Metastasis to the Lung	617
Sarcomas Metastasizing to the Lung.....	622
References	625
19 Molecular Pathology of Lung Tumors	633
Introduction.....	633
Therapy-Relevant Molecular Changes in	
Pulmonary Carcinomas	633
NSCLC and Angiogenesis ...	633
NSCLC and Cisplatin Drugs, the Effect of Antiapoptotic Signaling.....	634
Thymidylate Synthase Blocker	634
Receptor Tyrosine Kinases in Lung Carcinomas.....	635
TP53 the Tumor Suppressor Gene	636
Adenocarcinomas	636
Squamous Cell Carcinomas	643
Large Cell Carcinoma	645
Other Types of Large Cell Carcinomas	645
The Neuroendocrine Carcinomas	646
Salivary Gland Type Carcinomas	648
Sarcomatoid Carcinomas (SC)	649
Preneoplastic Lesions	650
When the Neoplastic Process Starts? And What to Analyze?	650
Hyperplasia of Goblet Cells and Squamous Metaplasia/Dysplasia	
.....	650
Genetic Aberrations in AAH	651
Neuroendocrine Cell Hyperplasia	651
Selected Examples of Benign Epithelial and Mesenchymal Lung Tumors	652
Benign Epithelial Tumors	652
Sclerosing Pneumocytoma ..	652
Tumors Induced by Mutations of the TSC Genes (Related to Tuberous Sclerosis)	652
Multifocal Nodular Pneumocyte Hyperplasia (MNPH)	653
Lymphangiomyomatosis (LAM)	653
Clear Cell Tumor (Sugar Tumor, PEComa = Perivascular Epithelioid Cell Tu mor)	653
Malignant Tumors of Childhood	653
Pleuropulmonary Blastoma.	653
Congenital Myofibroblastic Tumor	654
Final Remarks	654
References	654

20 Immunotherapy of Lung Tumors	671
References	682

21 Diseases of the Pleura	687
Hemorrhage.....	687
Effusion.....	687
Inflammation:Pleuritis.....	687
Purulent Pleuritis.....	688
Eosinophilic Pleuritis	688
HemorrhagicPleuritis	688
Chronic Pleuritis	688
Tumors	691
Mesothelioma.....	691
Adenomatoid Tumor	707
OtherTumorsofthe Pleura.....	707
SolitaryFibrousTumorof Pleura (Fibroma, SFT)	707
Desmoid Tumor	708
Calcifying(Fibrous)PleuraTumor (CPT).....	710
Primary Squamous Cell Carcinoma of Pleura	710
Primary Fibrosarcoma.....	711
Undifferentiated SarcomaArising in theLungand/orPleura(FormerlyMalignan t	
FibrousHistiocytoma, MFH).....	711
Desmoplastic Round CellTumor.....	711
Metastasis to the Pleura.....	711
References	714
22 LungTumorsinExperimentalModels	721
History.....	721
TobaccoInhalationExperiments.....	721
WhyAdenocarcinomas in Mice and Rats?	722
Cell Cultures of Lung Carcinomas	722
XenograftTransplantationofHumanCarcinomas/Cell Cultures into Nude Mice	723
OrganoidCultureSystems	723
DifferencesinChemicallyInducedLungTumors Compared to Humans.....	723
The Urethane Model	725
Genetically Engineered Mouse Models of Lung Cancer	725
The PulmonaryAdenocarcinoma Models.....	726
Histopathology of Adenocarcinomas	726
Immunohistochemistry as anAid to Identify the Precursor Cell Population	730
Progression of Adenocarcinomas	731
SpecificChangesInducedbyGenetic Modifications	732
DoMouseAdenocarcinomasResemble HumanAdenocarcinomas?	733
Differences in Mouse and Human LungMorphologyasExplanationforDiffer ent	
AdenocarcinomaAppearance	734

Genetic Differences between Mouse and Human Adenocarcinomas.....	735
Cellular Origin of Adenocarcinomas	735
The Small Cell Carcinoma Models	736
Models of Metastasis	738
References	738
23 Handling of Tissues and Cells	745
Biopsies.....	745
Videothoracoscopic Lung Biopsy (VATS) and Open Lung Biopsy (OLB)	745
Resection Specimen	746
Frozen Section Handling and Evaluation	746
Handling of Cells	748
Microbiology.....	749