

Jawahar L. Tiwari and Paul I. Terasaki

HLA and Disease Associations

With 23 Figures



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Preface

The human leukocyte antigen (HLA) or tissue types are the products of a rapidly developing field of knowledge within the last 20 years. In the early stages of the research many investigators suspected the existence of a complex series of transplantation antigens, but it was widely believed that these antigens would not be well-defined even in this century. Yet in the last two decades as many as 124 different HLA antigens determined by at least 7 very closely linked genes located on the short arm of chromosome 6 have been identified and subsequently agreed upon by an international nomenclature committee.¹ Extensive international collaboration fueled by the potential clinical application of these antigens to clinical transplantation has advanced the field rapidly. There were nine international histocompatibility workshops held during this period. Although identification of HLA antigens was of primary clinical importance in transplantation and of great basic interest in human genetics and anthropology,² a rather unexpected bonus has been the determination that HLA antigens are associated with disease susceptibility to a greater extent than any other known genetic marker in man.

In the past, many genetic polymorphisms have been suspected to be associated with diseases. The most extensively studied markers are blood groups, enzymes, and serum proteins. A comprehensive account of published studies, totalling approximately 1,000, of these markers is available in a book by Mourant et al.³ Aside from the extensive nature of these studies, one is struck by the data showing only very weak association of diseases with these markers. The relative risk in all of these reports has been less than 2. One of the most thoroughly investigated associations is that of carcinoma of the stomach with blood group A. Analysis of the data on 53,155 patients shows a relative risk of 1.22 indicating that a type A person is only 1.22 times more likely to develop stomach cancer than those who are not type A.³

In contrast, the association between HLA-B27 and ankylosing spondylitis has a relative risk of 69. There are many diseases in which relative risk value is greater than 2. Thus, the available data on HLA associations with diseases have far surpassed all the existing knowledge in this field. What is more remarkable is that HLA and disease associations were developed principally in the last 10 years during which approximately 4,000 articles have been published. This burst of activity occurred throughout the world in many different centers, as witnessed by the diverse sources of the bibliography. In many of these diseases the genetic

component had long been suspected but now for the first time it has become possible to actually find the genetic inheritance through a well-defined marker.

It was rather surprising that the strength of the association of HLA-B27 with ankylosing spondylitis, first described by our laboratory in 1973⁴ and by Brewerton et al.⁵ which had been the primary stimulus for the study of other diseases has, in fact, not been exceeded by the many other diseases that have been subsequently found to be associated with the HLA antigens. Thus among more than 530 diseases that have been studied in 4,000 publications, relative risk that is higher than that for ankylosing spondylitis has not been noted. To a certain extent this might be considered to have been somewhat of a disappointment because many of us had expected more diseases to have such a high association. In addition, some diseases that "theoretically" should have been associated with HLA have not yielded the expected association. Instead a rather obscure disease, ankylosing spondylitis, continues to be the disease with the strongest association.

Despite these disappointments, from the research work of the past 12 years, the actual degree of HLA association with various diseases is gradually becoming clear. Although a given single study may have overstated certain associations, there has now been time enough for their confirmation in many different laboratories and thus a more accurate picture of the degree of association is slowly emerging. In this book we have tried to stay close to the data published by the various authors and have refrained from too many interpretations. An attempt has been made for comprehensive coverage, even in instances where we have had suspicions that the data may not have been completely correct. Associations that are true tend to be validated by subsequent studies in other laboratories and those that are spurious are not confirmed in later reports. Important studies on important diseases tend to be followed up whereas findings that are too suspect tend not to be reinvestigated by others. Thus, we leave the reader to draw his conclusions from the comprehensive data presented in this book.

One of the highlights in the study of HLA and disease was an international symposium held in Paris in 1976.⁶ This volume presents many of the associations known up to that time, together with ideas on the mechanisms responsible for these associations. Reviews of the literature have been published by Braun in 1979⁷ and by Ryder et al.⁸ The present book is meant to be a comprehensive account in which all the articles published on HLA and diseases that we are aware of are included. Many of the studies demonstrating associations with the new HLA-DR locus antigens have been undertaken since the publication of the aforementioned reviews.

We hope that this book will serve as a reference for all those who may wish to initiate studies in this interesting area. We also hope that our colleagues will not be too harsh with us for not offering a study involving a resynthesis or strong interpretation of the literature. Our hope has been to make it easy for the reader to arrive at his own conclusions for each of the disease categories.

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In the later stages of this project it became necessary to utilize the flexibility and the convenience of a wordprocessor and also a letter-quality printer. In the laboratory these facilities were available only on the microcomputers and hence a new set of programs for these computers were written by Kevin Hanson, David Kandasamy, and Dennis Aoki. The final manuscript was produced by these programs.

Dr. Pawel Kaszubowski translated many of the papers without an English abstract and also helped in the interpretation of the clinical data in these reports. Dr. Sarina Cats has kindly read the entire manuscript and provided valuable comments.

The manuscript was typed by Pam Kaisaki and the editorial assistance was provided by Rita Loew.

Contents

| | |
|--|-------|
| Acknowledgments | xxiii |
| 1 HLA Nomenclature | 1 |
| 2 The HLA Complex | 4 |
| History | 4 |
| The Genes of the HLA Complex | 5 |
| Inheritance of HLA | 8 |
| Frequencies of HLA Antigens | 8 |
| Racial Variations in Antigen Frequencies | 9 |
| Cross-Reactivity | 13 |
| Linkage Disequilibrium | 13 |
| Typing Methodology | 14 |
| 3 The Data and Statistical Analysis | 18 |
| The Data | 18 |
| Population Data Analysis | 18 |
| Family Data Analysis | 22 |
| Diagnostic Value of HLA Typing | 24 |
| Interpretation of the Data and the Analysis | 25 |
| 4 Mechanisms of HLA and Disease Associations | 28 |
| General Background | 28 |
| Mechanisms | 28 |
| 5 Overview | 32 |
| Summary of the Most Significant Associations | 32 |
| HLA Antigens Associated with Diseases | 43 |
| 6 Rheumatology and Joint Diseases | 49 |
| Brachymetacarpia | 49 |
| Congenital Dislocation of Hip | 49 |
| Spina Bifida | 49 |
| Idiopathic Scoliosis | 51 |
| Ossification of Posterior Longitudinal Ligament of the Cervical Vertebrae | 51 |
| Dactylitis ("Sausage-Like" Toes) | 51 |

| | |
|---|---------|
| Hydroxyapatite Rheumatism (Calcific Periarthritis) | 52 |
| Low Back Pain | 52 |
| Chondrocalcinosis | 52 |
| Hereditary Chondrocalcinosis | 53 |
| Perthes' Disease | 54 |
| Paget's Disease | 54 |
| Frozen Shoulder | 55 |
| Arthritis (Unspecified) | 55 |
| Rheumatoid Arthritis | 55 |
| Juvenile Rheumatoid Arthritis | 64 |
| Malignant Rheumatoid Arthritis | 70 |
| Seronegative Pauciarticular Arthritis | 71 |
| Seronegative Peripheral Arthritis | 71 |
| Seronegative Chronic Polyarthritis | 72 |
| Gonococcal Arthritis | 72 |
| Psoriatic Arthropathy (Unspecified) | 72 |
| Psoriatic Arthropathy (Central) | 75 |
| Psoriatic Arthropathy (Peripheral) | 75 |
| Psoriatic Arthropathy (Peripheral and Sacroiliitis) | 76 |
| Post- <i>Yersinia</i> Arthritis | 80 |
| Postgonorrhoic Arthritis | 81 |
| Postshigellosis Arthritis | 81 |
| Postmeningococcal Arthritis | 82 |
| Postrubella Vaccination Arthropathy | 82 |
| Post- <i>Salmonella</i> Arthritis | 82 |
| Septic Arthritis Due to <i>Klebsiella</i> | 82 |
| Reactive Arthritis After <i>Campylobacter jejuni</i> Enteritis | 83 |
| Reactive Arthritis After <i>Mycoplasma pneumoniae</i> Infection | 83 |
| Sexually Acquired Reactive Arthritis | 83 |
| Pseudopolyarthritis of the Spine | 84 |
| Ankylosing Spondylitis | 85 |
| Ankylosing Spondylitis in Inflammatory Bowel Disease | 100 |
| Seronegative "Spondylitic Variant" Syndrome | 100 |
| Vertebral Ankylosing Hyperostosis (Forestier's Disease) | 101 |
| Sacroiliitis | 102 |
| Polyarthrosis of Hands | 103 |
| Mechanical Disorders of the Spine | 103 |
| Osteoarthritis | 104 |
| Osteitis Condensans Ilii | 104 |
| Juvenile Dermatomyositis | 104 |
| Caplan's Syndrome | 105 |
| Neurogenic Paraosteoarthropathy | 105 |
| Spondylarthritis in Chronic Brucellosis | 106 |
| Amyloidosis in Rheumatoid Arthritis | 107 |
| Gout | 107 |
| Reiter's Disease | 107 |
| 7 Dermatology | 112 |
| Psoriasis Vulgaris | 112 |
| Pustular Psoriasis | 127 |
| Guttate Psoriasis | 127 |
| Erythrodermic Psoriasis | 128 |

| | |
|--|------------|
| Persistent Palmoplantar Pustulosis (Pustulosis Palmaris et Plantaris) | 128 |
| Flexural Psoriasis (Psoriasis Inversus, Intertriginous Psoriasis) | 130 |
| Pemphigus Vulgaris | 130 |
| Pemphigus Foliaceus | 132 |
| Bullous Pemphigoid | 133 |
| Benign Mucosal Pemphigoid (Cicatrical Pemphigoid, Ocular Pemphigus) | 133 |
| Benign Familial Pemphigus (Hailey-Hailey's Disease) | 133 |
| Subacute Cutaneous Lupus Erythematosus | 134 |
| Discoid Lupus Erythematosus | 134 |
| Atopic Dermatitis | 135 |
| Atopy (Unspecified, Includes Eczema) | 135 |
| Dermatitis Herpetiformis | 136 |
| Psoriasiform Napkin Dermatitis | 139 |
| Seborrheic Dermatitis | 140 |
| Epidermolysis Bullosa | 140 |
| Vitiligo | 140 |
| Urticaria | 141 |
| Acne Conglobata | 142 |
| Alopecia Areata | 142 |
| Keloids and Hypertrophic Scars | 143 |
| Lichen Planus | 143 |
| Lichen Sclerosus et Atrophicus | 144 |
| Pityriasis Rubra Pilaris | 145 |
| Generalized Granuloma Annulare | 145 |
| Localized Granuloma Annulare | 145 |
| Kawasaki's Disease (Mucocutaneous Lymph Node Syndrome) | 145 |
| Behçet's Disease | 146 |
| Xeroderma Pigmentosum | 149 |
| Desquamative Erythroderma | 150 |
| Hutchinson-Guilford Progeria Syndrome | 150 |
| Werner's Syndrome | 150 |
| Keratoacanthoma | 150 |
| Felty's Syndrome | 150 |
| Goltz-Gorlin Syndrome (Dermal Hypoplasia) | 150 |
| Geographic Tongue | 151 |
| Erythema Multiforme | 151 |
| 8 Neurology | 152 |
| Multiple Sclerosis | 152 |
| Myasthenia Gravis | 167 |
| Spinocerebellar Ataxia | 174 |
| Friedreich's Ataxia | 174 |
| Muscular Dystrophy | 174 |
| Myotonic Dystrophy | 175 |
| Neurolathyrism | 175 |
| Chronic Relapsing Idiopathic Inflammatory Polyneuropathy (Guillain-Barré Type) | 175 |
| Guillain-Barré Syndrome | 175 |
| Bell's Palsy (Idiopathic Facial Palsy) | 176 |

| | |
|---|------------|
| Amyotrophic Lateral Sclerosis | 176 |
| Migraine | 177 |
| Cluster Headache | 178 |
| Infantile Spasms (West's Syndrome) | 178 |
| Epilepsy | 178 |
| Lennox-Gastaut Syndrome | 179 |
| Paraplegia and/or Guadriplegia | 179 |
| Parkinson's Disease | 179 |
| Motor Neuron Disease | 180 |
| Spinal Muscular Atrophy | 180 |
| Peroneal Muscular Atrophy (Charcot-Marie-Tooth Disease) | 181 |
| Ataxia-Telangiectasia | 181 |
| Huntington's Disease | 181 |
| Subacute Sclerosing Panencephalitis | 181 |
| Paralytic Dementia | 182 |
| Neurofibromatosis (Von Recklinghausen's Disease) | 182 |
| Idiopathic Torsion Dystonia | 182 |
| Syringomyelia | 183 |
| Sensorineural Hearing Loss | 183 |
| Anencephaly | 183 |
| Narcolepsy | 184 |
| 9 Endocrinology | 185 |
| Juvenile Diabetes Mellitus (Insulin Dependent) | 185 |
| Maturity-Onset Diabetes Mellitus (Insulin-Dependent) | 210 |
| Maturity-Onset Type Diabetes in Young (MODY) | 212 |
| Gestational Diabetes | 213 |
| Wolfram Syndrome | 213 |
| Glucose Intolerance After the Use of Low-Estrogen Oral Contraceptive | 213 |
| Glucose Intolerance After Renal Transplantation | 214 |
| Graves' Disease | 214 |
| Congenital Hypothyroidism | 220 |
| Subacute Thyroiditis (De Quervain) | 221 |
| Painless Thyroiditis | 222 |
| Hashimoto's Thyroiditis | 222 |
| Myxedema | 224 |
| Polyglandular Failure | 224 |
| Congenital Adrenal Hyperplasia Due to 11- β -Hydroxylase Deficiency | 225 |
| Congenital Adrenal Hyperplasia Due to 17- α -Hydroxylase Deficiency | 225 |
| Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency | 226 |
| Adrenocortical Hyperfunction | 229 |
| Idiopathic Addison's Disease | 229 |
| Kallman's Syndrome (Hypogonadotropic Hypogonadism and Anosmia) | 229 |
| Multiple Endocrine Adenomatosis (Type I) | 229 |
| Cushing's Syndrome | 230 |
| Aldosterone Biosynthetic Defect Due to Type 2 Corticosterone Methyl-Oxidase Deficiency | 230 |

| | |
|---|-----|
| Primary Ovarian Failure | 230 |
| Klinefelter's Syndrome | 231 |
| Transcortin Level in Serum | 231 |
| Testosterone Level in Serum | 231 |
| 10 Gastroenterology | 232 |
| Idiopathic Hemochromatosis | 232 |
| Celiac Disease | 236 |
| Wilson's Disease (Hepatolenticular Degeneration) | 242 |
| Alcoholic Liver Disease | 242 |
| Chronic Idiopathic Pancreatitis | 244 |
| Chronic Alcoholic Pancreatitis | 245 |
| Cryptogenic Cirrhosis of the Liver | 245 |
| Cirrhosis with Unknown Etiology | 246 |
| Chronic Active Drug-Induced Hepatitis | 246 |
| Chronic Active Hepatitis Without Hepatitis B Surface Antigen | 246 |
| Chronic Active Hepatitis with Hepatitis B Surface Antigen | 249 |
| Chronic Active Cryptogenic Hepatitis | 251 |
| Chronic Active Hepatitis (Unspecified) | 251 |
| Acute Hepatitis | 253 |
| Crohn's Disease | 253 |
| Crohn's Disease with Ankylosing Spondylitis | 255 |
| Crohn's Disease with Peripheral Arthritis | 256 |
| Ulcerative Colitis | 256 |
| Primary Biliary Cirrhosis | 258 |
| Immunoproliferative Small Intestinal Disease (Mediterranean Abdominal Lymphoma) | 259 |
| Pyloric Stenosis | 259 |
| Atrophic Gastritis | 259 |
| Duodenal Ulcer | 260 |
| Gastric Ulcer | 261 |
| Porphyria Cutanea Tarda | 261 |
| Gilbert's Syndrome | 262 |
| Acute Intermittent Porphyria | 262 |
| Intestinal Adenomatous Polyposis | 262 |
| Plummer-Vinson Stricture | 262 |
| Intrahepatic Cholestasis of Pregnancy | 263 |
| Primary Sclerosing Cholangitis | 263 |
| 11 Ophthalmology | 264 |
| Optic Neuritis | 264 |
| Acute Anterior Uveitis | 265 |
| Chronic Uveitis | 267 |
| Uveitis (Unspecified) | 267 |
| Primary Open-Angle Glaucoma | 268 |
| Acute Angle-Closure Glaucoma | 269 |
| Capsular Glaucoma | 269 |
| Pigmentary Glaucoma | 270 |
| Ocular Hypertension | 270 |
| Pigment Dispersion Syndrome | 270 |
| Eale's Disease | 271 |
| Stromal Dystrophy | 271 |

| | |
|---|------------|
| Fuchs' Endothelial Dystrophy | 271 |
| Keratoconus | 271 |
| Cogan's Syndrome | 271 |
| Scleritis | 272 |
| Toxoplasmic Retinochorioiditis | 272 |
| Retinitis Centralis Serosa (Central Serous Retinopathy) | 272 |
| Chorioretinitis | 273 |
| Senile Cataract | 273 |
| Steroid Induced Cataract | 273 |
| Juvenile Chronic Iridocyclitis | 273 |
| Adult Iridocyclitis | 273 |
| Degenerative Choroidopathy | 274 |
| Retinitis Pigmentosa | 274 |
| Rhegmatogenous Retinal Detachment | 274 |
| Sympathetic Ophthalmia | 275 |
| Birdshot Retinochoroidopathy | 275 |
| Pseudoexfoliation of the Lens Capsule | 275 |
| Thygeson's Superficial Punctate Keratitis | 275 |
| Hereditary Optic Atrophy | 276 |
| Adie's Syndrome | 276 |
| 12 Malignancy | 277 |
| Carcinoma of the Thyroid Gland | 277 |
| Carcinoma of the Mouth | 277 |
| Carcinoma of the Brain | 277 |
| Carcinoma of the Bladder | 278 |
| Carcinoma of the Prostate | 278 |
| Carcinoma of the Ovary | 279 |
| Carcinoma of the Uterus | 279 |
| Carcinoma of the Endometrium | 280 |
| Carcinoma of the Cervix | 280 |
| Carcinoma of the Breast | 281 |
| Carcinoma of the Lung and Larynx | 283 |
| Carcinoma of the Lung | 283 |
| Carcinoma of the Larynx | 285 |
| Carcinoma of the Pancreas | 285 |
| Carcinoma of the Liver | 285 |
| Carcinoma of the Rectum | 286 |
| Carcinoma of the Colon | 287 |
| Carcinoma of the Stomach | 288 |
| Carcinoma of the Esophagus | 288 |
| Carcinoma of the Pharynx | 289 |
| Carcinoma of the Nasopharynx | 289 |
| Carcinoma of the Salivary Gland | 290 |
| Carcinoma of the Pituitary Gland | 290 |
| Testicular Cancer | 290 |
| Renal Cell Carcinoma | 292 |
| Carcinoma (Unspecified) | 293 |
| Leukemia (Unspecified) | 293 |
| Granulocytic Leukemia | 294 |
| Chronic Myeloid Leukemia | 295 |
| Acute Myeloid Leukemia | 295 |

| | |
|---|---------|
| Acute Lymphatic Leukemia | 297 |
| Chronic Lymphatic Leukemia | 301 |
| Leukemic Reticuloendotheliosis (Hairy Cell Leukemia) | 302 |
| Lymphoma (Unspecified) | 303 |
| Follicular Lymphoma | 303 |
| Burkitt's Lymphoma | 304 |
| Glioblastoma | 304 |
| Neuroblastoma | 304 |
| Retinoblastoma | 305 |
| Uveal Melanoblastoma | 306 |
| Melanoma | 306 |
| Malignant Choroidal Melanoma | 308 |
| Lymphosarcoma | 308 |
| Reticulosarcoma | 309 |
| Liposarcoma | 309 |
| Ewing's Sarcoma | 309 |
| Osteosarcoma | 309 |
| Kaposi's Sarcoma | 310 |
| Trophoblastic Neoplasms | 310 |
| Choriocarcinoma | 311 |
| Waldstrom's Macroglobulinemia | 311 |
| Thymoma | 311 |
| Colorectal Adenoma | 311 |
| Multiple Myeloma | 312 |
| Mycosis Fungoides | 313 |
| Hodgkin's Disease | 314 |
| Glioma | 320 |
| Pheochromocytoma | 320 |
| Sipple's Syndrome | 320 |
| Wilms' Tumor | 320 |
| 13 Allergy | 322 |
| Allergy to Insulin | 322 |
| Allergy to Cow's Milk | 322 |
| Allergy to Dust | 322 |
| Allergy to Nickel | 323 |
| Allergy to Chromium | 324 |
| Allergy to Rye | 324 |
| Allergy to Ragweed | 324 |
| Allergy to Aspergillus (Allergic Bronchopulmonary Aspergillosis) | 326 |
| Allergy to <i>Alternaria Tenuis</i> | 327 |
| Allergy to Formalin | 327 |
| Allergy to Balsam of Peru | 327 |
| Allergy to Colophony | 327 |
| Allergy to Wool Alcohols | 327 |
| Allergy to Para Group Compounds | 327 |
| Allergy to Cat Dander | 328 |
| Pigeon Breeder's Lung | 328 |
| Farmer's Lung | 328 |
| Silicosis | 328 |
| Asbestosis | 329 |

| | |
|---|------------|
| Cedar Pollinosis | 329 |
| Grass Pollinosis | 330 |
| Flax Byssinosis | 330 |
| Coalworker's Pneumoconiosis | 331 |
| Avian Hypersensitivity | 331 |
| Cryptogenic Fibrosing Alveolitis | 332 |
| Idiopathic Pulmonary Fibrosis | 332 |
| IgE Levels in Healthy Individuals | 333 |
| Hay Fever | 333 |
| Schonlein-Henoch Nephritis | 333 |
| Sensitivity to the Odor of Androstenone | 333 |
| 14 Urogenital Diseases | 335 |
| Herpes Gestationis | 335 |
| Habitual Abortion | 335 |
| Eclampsia | 337 |
| Preeclampsia | 337 |
| Infertility (Unexplained) | 338 |
| Peyronie's Disease | 339 |
| Balanitis | 339 |
| Azoospermia | 340 |
| Ureteropelvic Junction Stenosis | 340 |
| Vesicoureteral Reflux | 340 |
| Mesangial IgA Glomerulonephritis (Berger's Disease) | 341 |
| Chronic Glomerulonephritis | 343 |
| Acute Poststreptococcal Glomerulonephritis | 343 |
| Idiopathic Membranous Nephropathy | 344 |
| Balkan Endemic Nephropathy | 344 |
| Nephrotic Syndrome | 346 |
| Steroid-Responsive Nephrotic Syndrome of Childhood | 346 |
| Renal Patients Without Hepatitis B Surface Antigens | 348 |
| Renal Patients Transiently Carrying Hepatitis B Surface Antigens | 348 |
| Renal Patients Persistently Carrying Hepatitis B Surface Antigens | 348 |
| Transplant Patients Carrying Hepatitis B Surface Antigens | 349 |
| Polycystic Kidneys | 349 |
| Retroperitoneal Fibrosis | 350 |
| Uremia | 350 |
| Essential Mixed Cryoglobulinemia | 350 |
| Benign Hematuria | 351 |
| Chronic Prostatitis | 351 |
| Pustular Bacterid of Andrews | 351 |
| 15 Cardiovascular Diseases | 352 |
| Rheumatic Fever | 352 |
| Rheumatic Heart Disease | 352 |
| Rheumatic Fever and Rheumatic Heart Disease | 353 |
| Ischemic Heart Disease | 354 |
| Essential Hypertension | 354 |
| Hypertrophic Cardiomyopathy | 355 |

| | |
|---|------------|
| Alcoholic Cardiomyopathy | 356 |
| Buerger's Disease | 356 |
| Atherosclerosis | 357 |
| Aortic Valve Disorders | 358 |
| Myocardial Infarction | 358 |
| Mitral Valve Prolapse | 358 |
| Aortitis Syndrome | 359 |
| Congenital Heart Malformation | 359 |
| Coronary Artery Disease | 360 |
| Complete Heart Block | 360 |
| Polyarteritis Nodosa | 360 |
| Churg-Strauss Vasculitis | 360 |
| Thrombophlebitis of Leg | 361 |
| Venous Thromboembolism | 361 |
| Varicose Veins of Lower Extremities | 361 |
| Varicocele | 361 |
| Idiopathic Portal Hypertension | 362 |
| Raynaud's Phenomenon | 362 |
| 16 Connective Tissue Diseases | 363 |
| Systemic Lupus Erythematosus | 363 |
| Hydralazine-Induced Systemic Lupus Erythematosus | 369 |
| Sjögren's Syndrome (Sicca Syndrome) | 369 |
| Scleroderma | 371 |
| Mixed Connective Tissue Disease | 373 |
| Polymyositis | 373 |
| Dermatomyositis | 374 |
| Hereditary Hemorrhagic Telangiectasia | 374 |
| Vasculitis (Venulitis) | 374 |
| Wegener's Granulomatosis | 374 |
| Polymyalgia Rheumatica | 375 |
| Temporal Arteritis (Giant Cell Arteritis, Horton's Disease) | 375 |
| Takayasu's Disease | 377 |
| Eosinophilic Fasciitis | 378 |
| CREST Syndrome | 378 |
| 17 Pulmonary Diseases | 379 |
| Asthma | 379 |
| Emphysema | 380 |
| Goodpasture's Syndrome | 380 |
| Sarcoidosis | 380 |
| Kartagener's Syndrome | 382 |
| Pulmonary Apical Fibrocystic Disease | 382 |
| 18 Infectious Diseases | 383 |
| Leprosy | 383 |
| Tuberculosis | 386 |
| Syphilis | 387 |
| Gonorrhea | 388 |
| Veneral Urethritis | 388 |
| Urethritis (Nonspecific and Nongonococcal) | 388 |
| Presumed Ocular Histoplasmosis | 388 |
| Tetanus | 389 |

| | |
|---|-----|
| Mononucleosis | 389 |
| Congenital Rubella | 390 |
| Aseptic Meningitis | 390 |
| Paralytic Poliomyelitis | 390 |
| Hemophilus Influenza Type B Infection | 391 |
| Recurrent Herpes Labialis | 392 |
| Recurrent Corneal Herpes (Herpetic Keratitis) | 393 |
| Recurrent Herpes Progenitalis (HSV-2) | 394 |
| Chronic Brucellosis | 394 |
| Infection by <i>Schistosoma Mansoni</i> | 395 |
| Vogt-Koyanagi-Harada Syndrome | 395 |
| Healthy Hepatitis B Surface Antigen Carriers | 396 |
| Meningococcal Meningitis | 398 |
| Meningococcal Infection | 398 |
| Jacob-Creutzfeldt Disease | 398 |
| Infection with Measles | 399 |
| Infection with Rubella Virus | 399 |
| Dengue Hemorrhagic Fever | 399 |
| Mumps | 399 |
| Paracoccidioidomycosis | 400 |
| Filariasis | 400 |
| Scabies | 400 |
| Amyloidosis | 401 |
| Thalassemia | 401 |
| 19 Musculoskeletal Diseases | 402 |
| Tendinous Calcifications | 402 |
| Iron-Overload-Associated Myopathy | 402 |
| Dupuytren's Contracture | 403 |
| 20 Psychiatric Diseases | 404 |
| Schizophrenia | 404 |
| Manic-Depressive Disorder | 408 |
| Psychosis Proto-Infantilis | 412 |
| Chronic Alcoholism | 412 |
| Alzheimer's Disease | 412 |
| Multiple Infarct Dementia | 414 |
| Autism | 414 |
| Narcotic Dependence | 414 |
| Tourette Syndrome | 414 |
| 21 Hematologic Diseases | 415 |
| Aplastic Anemia | 415 |
| Fanconi's Anemia | 415 |
| Pernicious Anemia | 416 |
| Idiopathic Autoimmune Hemolytic Anemia | 418 |
| Congenital Neutropenia | 418 |
| Chronic Familial Neutropenia | 419 |
| Autoimmune Thrombocytopenic Purpura | 419 |
| Idiopathic Thrombocytopenic Purpura | 420 |
| Paroxysmal Nocturnal Hemoglobinuria | 421 |
| Thalassemia Minor | 421 |
| Erythrocyte Glucose-6-Phosphate Dehydrogenase (G-6-PD) Deficiency | 421 |