

Contents

1	Historical Concepts of Immune Hemolytic Anemias	1
	THE LESSONS OF HISTORY	1
	EARLIEST DESCRIPTIONS OF POSSIBLE ACQUIRED HEMOLYTIC ANEMIA	2
	EARLY EXPERIMENTAL INVESTIGATION OF BLOOD	2
	RED BLOOD CELL AGGLUTINATION	4
	FIRST DESCRIPTION OF HEMOLYTIC ANEMIA	5
	THE DISTINCTION BETWEEN CONGENITAL AND ACQUIRED HEMOLYTIC ANEMIAS	5
	DESCRIPTION OF SPHEROCYTES AND ANALYSIS OF THEIR SIGNIFICANCE	7
	OSMOTIC FRAGILITY OF RED BLOOD CELLS	8
	RETICULOCYTES	9
	THE CONCEPTS OF IMMUNE HEMOLYSIS AND <i>HORROR AUTOTOXICUS</i>	10
	THE FIRST DESCRIPTION OF AN AUTOIMMUNE HEMOLYTIC ANEMIA	11
	EARLY DIAGNOSTIC TESTS FOR PAROXYSMAL COLD HEMOGLOBINURIA	12
	THE DONATH-LANDSTEINER DISCOVERY, 1904: THE FIRST DESCRIPTION OF AN AUTOANTIBODY AND OF AN AUTOIMMUNE HUMAN DISEASE	12
	FURTHER STUDIES ON THE MECHANISMS OF HEMOLYTIC ANEMIA AND OBSERVATIONS ON THE DISTINCTION BETWEEN CONGENITAL AND ACQUIRED FORMS	13
	THE ROLE OF THE SPLEEN AND THE EFFECT OF SPLENECTOMY	14
	FURTHER CHARACTERIZATION OF HEMOLYTIC ANEMIAS	15
	MEASUREMENTS OF RED BLOOD CELL SURVIVAL	17
	THE ANTIGLOBULIN (COOMBS') TEST	20
	THE CONCEPT OF AUTOIMMUNE HEMOLYTIC ANEMIA	23
	RADIOACTIVE CHROMIUM (^{51}CR) AND DF^{32}P	24
	COLD AGGLUTININ SYNDROME	24
	MORE RECENT EVENTS	26
	HISTORICAL NOTES REGARDING HEMOLYTIC TRANSFUSION REACTIONS	26
	FIRST RECORDS OF TRANSFUSIONS	26
	THE FIRST RECORD OF HEMOLYTIC TRANSFUSION REACTIONS	26
	NATIONAL AND INTERNATIONAL CONTROVERSY	28
2	The Diagnosis of Hemolytic Anemia	33
	DEFINITIONS	33
	Hemolysis/	33
	Compensated Hemolytic Disease/	33
	Anemia with a Hemolytic Component/	33
	Hemolytic Anemia/	33
	Acquired Hemolytic Anemia/	33
	Hereditary Hemolytic Anemias/	34
	Congenital Hemolytic Anemias/	34

Intravascular Hemolysis/	34
Extravascular Hemolysis/	34
DETERMINATION OF THE HEMOLYTIC NATURE OF AN ANEMIA	35
The Blood Count/	35
Reticulocytes/	36
RBC Morphology/	42
Bilirubin/	42
Serum Haptoglobin/	43
Serum Lactic Dehydrogenase/	45
Transfusion Requirement/	46
Intravascular Hemolysis/	48
Hemopexin and Methemalbumin/	49
Hemosiderinuria/	49
Other Tests/	50
Summary and Comments Concerning the Value of Laboratory Tests to Determine the Presence of Hemolysis/	50
ESTABLISHING A TENTATIVE DIAGNOSIS OF THE CAUSE OF THE HEMOLYTIC ANEMIA	51
History and Physical Examination/	51
The Peripheral Blood Film/	53
Intravascular Hemolysis/	58
The Direct Antiglobulin Test/	58
SPECIFIC CONFIRMATORY TESTS	58

Classification and Clinical Characteristics of Autoimmune Hemolytic Anemias 61

CLASSIFICATION	61
CLINICAL CHARACTERISTICS OF AUTOIMMUNE HEMOLYTIC ANEMIAS	62
Warm Antibody AIHA/	62
Incidence/	62
Age Distribution/	63
Sex Distribution/	63
Clinical Manifestations/	63
Physical Signs/	64
The Blood Picture/	66
Bone Marrow Findings/	69
Reticulocytes/	69
Prognosis and Survival/	70
Recovery from AIHA/	71
Cold Agglutinin Syndrome/	71
Incidence/	71
Age and Sex Distribution/	71
Symptoms and Signs/	71
Laboratory Findings/	72
Course and Prognosis/	73
Management/	73
Paroxysmal Cold Hemoglobinuria/	73
Incidence/	73
Classification/	74
Race, Sex, and Age Distribution/	74
Idiopathic and Secondary Types/	74
Symptoms and Signs/	75
Hematologic Findings/	75
Laboratory Diagnosis/	76
Chronic Paroxysmal Cold Hemoglobinuria/	77
Treatment and Prognosis/	78
Combined Cold and Warm AIHA or "Mixed" AIHA/	79
Case Reports/	79
Secondary Cold and Warm AIHA/	81

Cautions Concerning the Diagnosis of Cold and Warm AIHA/	81
Clinical Course/	81
Management/	81
AIHA Associated with a Negative DAT/	82
Secondary Autoimmune Hemolytic Anemias/	82
Relative Incidence of Idiopathic and Secondary Types of Warm Antibody AIHA/	82
Ovarian Tumors/	83
Ulcerative Colitis/	84
Lymphoproliferative Disorders/	88
Systemic Lupus Erythematosus/	94
Collagen Disorders Other Than SLE/	96
Thymoma/	96
AIHA and Carcinoma/	97
AIHA after Vaccination/	97
AIHA and Infectious Agents/	99
Primary Immunodeficiency Diseases/	110
Autoimmune Lymphoproliferative Syndrome/	112
Miscellaneous Disorders Reported in Association with AIHA/	112
Secondary Cold Agglutinin Syndrome/	113
Infectious Diseases/	113
Waldenström's Macroglobulinemia/	113
Nonhematologic Malignancies and Cold Agglutinin Syndrome/	114

4 Mechanisms of Immune Hemolysis 133

INTRAVASCULAR IMMUNE RED CELL DESTRUCTION 133

Complement Activation/ 134

The Classical Pathway of Complement Activation/ 134

The Alternative Pathway of Complement Activation/ 138

The Mannose-Binding Lectin Pathway of Complement Activation/ 140

In Vivo Effects of Red Cell-Bound Complement/ 140

EXTRAVASCULAR IMMUNE RED CELL DESTRUCTION 141

Macrophage Receptors/ 141

Complement Receptors/ 144

Macrophage Interactions with RBCs Coated with Immunoglobulin and/or Complement/ 145

OTHER POSSIBLE MECHANISMS OF IMMUNE RED CELL DESTRUCTION 158

Possible Role of Cells Other Than Macrophages in Immune Red Cell Destruction/ 158

Lymphocytes/ 158

NK Cells/ 158

Neutrophils/ 159

Destruction of "Innocent Bystander" Red Cells (Bystander Lysis)/ 159

Role of Armed Macrophages in Immune Destruction of Red Cells and Platelets/ 160

In Vivo Agglutination of Red Cells/ 161

5 Differential Diagnosis of Immune Hemolytic Anemias 167

DISTINCTIVE CLINICAL AND ROUTINE LABORATORY FEATURES 167

LABORATORY DIAGNOSIS OF IMMUNE HEMOLYTIC ANEMIAS 169

Significance of the DAT in the Differential Diagnosis of Immune Hemolytic Anemias/ 169

Results Using Polyspecific and Monospecific Antiglobulin Reagents in Patients with AIHAs/ 170

An Approach to the Characterization of Antibodies in the Serum and Eluates from RBCs of Patients with AIHA/ 177

Characteristic Serology of WAIHA/ 178

WAIHA Associated with IgM Autoantibodies/ 180

Characterization of Antibodies in the Cold Agglutinin Syndrome/ 182

Development of Criteria to Distinguish Benign Cold Agglutinins from Those Associated with In Vivo Hemolysis/ 183

Essential Diagnostic Tests for CAS/ 186

Immunochemistry and Molecular Analysis of Cold Agglutinins Associated with CAS/188

IgG and IgA Cold Autoagglutinins/190

Patients Who Have Warm and Cold Autoantibodies/191

Laboratory Diagnosis of Paroxysmal Cold Hemoglobinuria (PCH)/191

Essential Diagnostic Tests/191

Cautions Regarding the Interpretation of the Donath-Landsteiner Test/193

Performing the Donath-Landsteiner Test in Patients with Hemoglobinemia/194

Comparison of Paroxysmal Cold Hemoglobinuria and the Cold Agglutinin Syndrome/194

Autoantibodies with Unusual Characteristics in Patients Who Have Been Diagnosed as Having PCH/195

6 The Serological Investigation of Autoimmune Hemolytic Anemia 201

THE ANTIGLOBULIN TEST 202

Principles of the Antiglobulin Test/202

Significance of a Positive DAT/203

IgG and Complement on RBCs of DAT-Negative Healthy Individuals/204

Seemingly Healthy Individuals with Positive DATs Due to IgG and/or C3 Sensitization/206

Clinical Significance of Positive DATs in Patients/207

AIHA Associated with a Negative DAT/208

Detecting Small Amounts of RBC-Bound IgG (and IgA and IgM) Using Flow Cytometry/208

Standardization of Anticomplement AGS/211

DAILY QUALITY CONTROL OF AGS/212

Detecting Low-Affinity Autoantibodies with a Cold Low Ionic Strength Saline Wash DAT/213

Standardization of IgG Subclass Antisera for Use with Sensitized RBCs/213

GENERAL SEROLOGIC INVESTIGATIONS 214

Collection of Blood/214

Determining the Blood Group of DAT-Positive Patients/214

Phenotyping DAT+ RBCs When Spontaneous Agglutination Occurs or When Using Antiglobulin Reactive Antisera/215

SEROLOGIC INVESTIGATIONS TO HELP IN THE DIFFERENTIAL DIAGNOSIS OF AIHA 217

DAT/217

Serum Screen to Determine Serum Antibody(ies) Characteristics/219

Cold Agglutinin Titer/Thermal Amplitude/Ii Specificity/220

TITRATION OF HEMOLYSINS/223

Donath-Landsteiner (DL) Test/223

DETERMINING SPECIFICITY OF AUTOANTIBODIES 224

Determining Specificity of Autoantibodies Associated with Warm Type Autoimmune Hemolytic Anemia/225

Determining Specificity of Autoantibodies Associated with Cold Agglutinin Syndrome 226

Determining Specificity of Autoantibodies Associated with Paroxysmal Cold Hemoglobinuria 227

7 Specificity of Autoantibodies 231

SPECIFICITIES ASSOCIATED WITH WARM-ANTIBODY TYPE AUTOIMMUNE HEMOLYTIC ANEMIA 231

SPECIFICITIES ASSOCIATED WITH GLYOPHORINS 234

SPECIFICITIES ASSOCIATED WITH THE KELL SYSTEM 236

SPECIFICITIES ASSOCIATED WITH THE KIDD AND DUFFY SYSTEMS 237

SPECIFICITIES ASSOCIATED WITH ABO AND Hh SYSTEMS 238

MISCELLANEOUS TARGETS FOR 37°C REACTIVE AUTOANTIBODIES 238

"MIMICKING ANTIBODIES" 239

CHANGES IN SPECIFICITY OF AUTOANTIBODIES 242

SPECIFICITIES NOT ASSOCIATED WITH BLOOD GROUP ANTIGENS 243

SPECIFICITIES ASSOCIATED WITH COLD AGGLUTININ SYNDROME	245
<i>i</i> Blood Group Antigens and Antibodies/	246
"Cold" Autoantibody Specificities Other Than Anti- <i>I</i> and Anti- <i>i</i> /	249
MISCELLANEOUS TARGETS FOR COLD AUTOANTIBODIES	251
OPTIMAL REACTIONS WITH STORED OR "OLD" RBCS	253
AUTOANTIBODY SPECIFICITY ASSOCIATED WITH PAROXYSMAL COLD	
HEMOGLOBINURIA	254

8 Drug-Induced Immune Hemolytic Anemia 261

INTRODUCTION	261
THE IMMUNE RESPONSE TO DRUGS	263
The Hapten Hypothesis/	265
The Immune Response to Penicillin/	266
The Immune Complex Hypothesis/	267
RBC Autoantibodies Induced by Drugs/	272
Newer Concepts of the Immune Response to Drugs Associated with Cytopenias/	275
Problems with the Unifying Hypothesis/	276
SUGGESTED MECHANISMS OF DRUG-INDUCED HEMOLYTIC ANEMIA AND/OR POSITIVE	
DIRECT ANTIGLOBULIN TESTS	278
Penicillin-type Mechanism/	278
Nonpenicillin-type Mechanism ("Immune Complex" Mechanism)/	279
Drug-Induced Nonimmunologic Adsorption of Protein onto RBCs/	279
Nonimmunologic Uptake of Protein by RBCs as a Possible Cause of	
Hemolytic Anemia/	282
SEROLOGIC AND CLINICAL FINDINGS ASSOCIATED WITH DIIHA	283
Drug-Dependent Antibodies/	284
Penicillin Antibodies/	284
DIIHA Associated with Penicillins Other Than Penicillin G/	286
Drug-Dependent Antibodies Other Than "Penicillin Type" ("Immune Complex" Mechanism)/	287
Drug-Independent Antibodies/	287
Laboratory and Clinical Findings Associated with Methyldopa Administration/	288
DIAGNOSIS OF DRUG-INDUCED AIHA	290
BLOOD TRANSFUSION	291
AIHA CAUSED BY DRUGS OTHER THAN METHYLDOPA	291
IMMUNE HEMOLYTIC ANEMIA AND/OR POSITIVE DIRECT ANTIGLOBULIN TESTS	
ASSOCIATED WITH THE CEPHALOSPORINS	293
USEFUL SEROLOGICAL METHODS FOR INVESTIGATING DIIHA	303

9 Unusual Aspects of Immune Hemolytic Anemias 319

A. Autoimmune Hemolytic Anemia with a Negative Direct Antiglobulin Test (DAT)	319
INCIDENCE OF DAT-NEGATIVE WARM ANTIBODY AIHA	319
RELATIONSHIP OF ANTIBODY CONCENTRATION TO RATE OF HEMOLYSIS	320
SENSITIVITY OF THE DAT	321
MEASUREMENT OF SMALL AMOUNTS OF RBC-BOUND IgG	321
DAT-NEGATIVE AIHA ASSOCIATED WITH LOW-AFFINITY IgG AUTOANTIBODIES	329
DAT-NEGATIVE AIHA ASSOCIATED WITH RBC-BOUND IgA AND IgM	330
SEROLOGICAL AIDS IN DIAGNOSING DAT-NEGATIVE AIHA	332
Could DAT-Negative AIHA Be Due to an Antibody-Independent, Cell-Mediated,	
Cytotoxicity Mechanism?/	334
THERAPY AND COURSE	334
B. Development of RBC Autoantibodies and AIHA Following Transfusion	335
DATA FROM ANIMAL EXPERIMENTATION	335
DATA FROM HUMANS	336

RETROSPECTIVE REVIEWS OF MULTIPLY TRANSFUSED PATIENTS	337
IMMUNOLOGICAL DATA	338
THE SOURCE OF AUTOANTIBODIES FOLLOWING TRANSFUSION	339
C. Autoimmune Hemolytic Anemia in Infancy and Childhood	341
CLINICAL FINDINGS AND COURSE	341
LABORATORY FINDINGS	342
AIHA OCCURRING AT A VERY EARLY AGE	343
Management/	343
PROGNOSIS	344
D. Autoimmune Hemolytic Anemia during Pregnancy	345
MATERNAL FINDINGS	345
OUTCOME OF PREGNANCIES	346
NEONATAL HEMOLYSIS	347
INFANTS WITHOUT HEMOLYSIS	347
HEMOLYTIC ANEMIA OF PREGNANCY WITH A NEGATIVE DIRECT ANTIGLOBULIN TEST AND FREQUENT RECURRENCES	347
MANAGEMENT	349
E. Familial Autoimmune Hemolytic Anemia	351
F. Cardiac Surgery and Cold Autoantibodies	352
ADVERSE EVENTS	352
IDENTIFICATION OF PATIENTS AT RISK	354
PATIENTS WITH COLD AGGLUTININS WHO DO NOT APPEAR TO BE AT RISK	354
MANAGEMENT	355
G. Differentiating Delayed Hemolytic Transfusion Reactions from Autoimmune Hemolytic Anemia	356
DIAGNOSTIC AIDS	356
Comparison of DAT and IAT/	357
Antibody Specificity/	357
Additional Approaches/	357
H. Bystander Immune Hemolysis	358
THE CONCEPT OF BYSTANDER IMMUNE CYTOLYSIS	358
Definition of Bystander Immune Cytolysis/	358
A BRIEF HISTORY OF THE DEVELOPMENT OF THE CONCEPT OF BYSTANDER IMMUNE CYTOLYSIS	358
CLINICAL SETTINGS IN WHICH BYSTANDER IMMUNE CYTOLYSIS MAY OCCUR	359
POSSIBLE MECHANISMS OF BYSTANDER IMMUNE CYTOLYSIS	361

10 Blood Transfusion in Autoimmune Hemolytic Anemias	375
ASSESSING THE NEED FOR TRANSFUSION IN PATIENTS WITH AUTOIMMUNE HEMOLYTIC ANEMIA	375
Reluctance to Transfuse Patients with AIHA/	376
Assessing the Acuteness of Onset and Rapidity of Progression of AIHA/	376
THE APPROPRIATE USE OF BLOOD IN VARIOUS CLINICAL SETTINGS IN PATIENTS WITH AIHA	376
THE RISKS OF TRANSFUSION IN PATIENTS WITH AUTOIMMUNE HEMOLYTIC ANEMIA	378
Risks Caused by the Patient's Autoantibody/	378
Risks Caused by Alloantibodies/	378
Risks Caused by the Increase in RBC Mass as a Result of Transfusion/	378
COMPATIBILITY TESTING IN WARM ANTIBODY AIHA	378
Red Cell Phenotyping and Genotyping/	378
Detection of Alloantibodies/	379
The Incidence of Alloantibodies in Patients with AIHA Who Require Transfusion/	379

Methods for Detection of RBC Alloantibodies in Patients with Autoantibodies/	379
Autoantibody Specificity/	385
"Least Incompatible Units"/	386
Autoimmune Hemolytic Anemia Without Serum Autoantibody/	387
The Optimal Frequency of Tests for Alloantibodies in a Patient with AIHA Who Is Transfused Repeatedly/	387
The Use of Phenotypically Matched RBCs for Transfusion/	388
COMPATIBILITY TESTING IN COLD ANTIBODY AIHAs	389
Cold Agglutinin Syndrome/	389
Paroxysmal Cold Hemoglobinuria/	391
OPTIMAL VOLUME OF BLOOD TO BE TRANSFUSED	391
IN VIVO COMPATIBILITY TESTING	394
THE USE OF WARM BLOOD FOR PATIENTS WITH COLD AGGLUTININ SYNDROME AND PAROXYSMAL COLD HEMOGLOBINURIA	395
THE USE OF RBC SUBSTITUTES	395
USE OF LEUKOCYTE-REDUCED RBCs	396
USE OF WASHED RBCs	396
AUTOLOGOUS BLOOD TRANSFUSION IN AIHA	396

11 Management of Autoimmune Hemolytic Anemias 401

WARM ANTIBODY AUTOIMMUNE HEMOLYTIC ANEMIA 401

Corticosteroid Therapy/401

Initial Management/ 401

High-Dose Corticosteroid Therapy/ 402

Subsequent Management/ 403

Long Term Results/ 403

Alternate-Day Therapy/ 404

Mechanisms of Action/ 404

Adverse Effects of Corticosteroid Therapy/ 405

Splenectomy/407

Indications/ 407

Surgical Technique/ 407

Clinical Response/ 408

*Durability of Responses Following Splenectomy/*409

Mechanisms of Response to Splenectomy/ 410

Prediction of Responses to Splenectomy/ 410

Adverse Effects of Splenectomy/ 411

Splenic Irradiation/416

Immunosuppressive Drugs/416

Danazol/ 423

Complement Inhibitors/ 424

Intravenous Immunoglobulin (IVIG)/ 424

Plasma Exchange/ 429

Hematopoietic Stem Cell Transplantation/ 431

Thymectomy/ 433

COLD AGGLUTININ SYNDROME 433

Avoidance of Cold/ 433

Corticosteroid Therapy/ 435

Immunosuppressive Drugs/ 436

Plasma Exchange/ 439

Splenectomy/ 439

Intravenous Immunoglobulin (IVIG)/ 440

Danazol/ 440

Therapeutic Failures/ 440

PAROXYSMAL COLD HEMOGLOBINURIA 441

SECONDARY AUTOIMMUNE HEMOLYTIC ANEMIAS 441

Chronic Lymphocytic Leukemia/ 441

HTRs ASSOCIATED WITH SICKLE CELL DISEASE (SCD)	547
The Sick Cell Hemolytic Transfusion Reaction Syndrome/	547
The Mechanism Underlying Post-transfusion Fall in Hemoglobin to Values Lower Than the Pretransfusion Values/	552
Management of Patients with the Sick Cell HTR Syndrome/	555
PATHOPHYSIOLOGY OF HTRs	555
Interrelationships of Mediators of the Inflammatory Response/	556
Disseminated Intravascular Coagulation Associated with HTRs/	557
Renal Failure Associated with HTRs/	557
Treatment of HTRs/	558
VARIATION IN CLINICAL SYMPTOMS ASSOCIATED WITH ABO-INCOMPATIBLE HTRs	558
FATALITIES DUE TO HTRs	559
HEMOLYTIC TRANSFUSION REACTIONS DUE TO ANTIBODIES THAT ARE NOT DETECTABLE BY ROUTINE PROCEDURES	563
HTRs ASSOCIATED WITH PASSIVELY TRANSFUSED ALLOANTIBODIES	566
LABORATORY INVESTIGATION OF HTRs	567
Index	573