

# Contents

List of Abbreviations . . . . . XXVII

## Screening and Toxicity of Anti-Inflammatory Drugs

### CHAPTER 19

**Screening and Assessment of the Potency of Anti-Inflammatory Drugs in vitro.**  
R. J. GRYGLEWSKI. With 3 Figures

A. Introduction . . . . . 3

B. Interaction With Non-Enzymic Proteins . . . . . 3

    I. Binding to Plasma Proteins . . . . . 3

        1. Displacement Reactions . . . . . 4

        2. Disulphide Interchange Reactions . . . . . 4

        3. Protection Against Protein Denaturation . . . . . 4

        4. Fibrinolytic Activity . . . . . 5

    II. Interaction With Biological Membranes . . . . . 5

        1. Effects on Erythrocyte Membrane . . . . . 5

        2. Effects on Lysosomal Membrane . . . . . 6

        3. Cytotoxic Properties . . . . . 7

        4. Effects on Leucocyte Migration . . . . . 8

C. Interaction With Enzymic Proteins . . . . . 8

    I. General Considerations . . . . . 8

    II. Interaction With Enzymes Involved in Carbohydrate, Protein, and Nucleic Acid Metabolism . . . . . 9

        1. Carbohydrate, Protein, and Amino Acid Metabolism . . . . . 9

        2. Nucleic Acid and Nucleotide Metabolism . . . . . 9

    III. Inhibition of Prostaglandin Synthetase . . . . . 10

        1. Prostaglandin Synthetase System . . . . . 10

        2. Assay of Prostaglandin Synthetase Activity . . . . . 11

        3. Prostaglandin Synthetase Inhibitors . . . . . 15

        4. Inhibition of Platelet Aggregation . . . . . 21

        5. Effects on Smooth Muscle . . . . . 25

D. Conclusions . . . . . 26

References . . . . . 27

## CHAPTER 20

**Inhibition of Erythema and Local Hyperthermia.** K. F. SWINGLE, R. J. TRANCIK, and D. C. KVAM. With 4 Figures

A. Introduction . . . . .	44
B. Ultraviolet (UV) Light and the Erythematous Response . . . . .	45
C. Instrumentation . . . . .	47
I. Light Sources for Induction of Erythema . . . . .	47
II. Measurement of Erythema and Local Hyperthermia . . . . .	47
1. Erythema . . . . .	47
2. Skin Temperature . . . . .	47
D. Procedures . . . . .	50
I. Erythema . . . . .	50
1. UV-Induced . . . . .	50
2. Thurfyl Nicotinate-Induced . . . . .	54
3. Miscellaneous Procedures for Producing Erythema . . . . .	54
II. Local Hyperthermia . . . . .	55
1. Local Hyperthermia in Paws of Rats Injected With Irritants . . . . .	56
2. Local Hyperthermia in UV-Irradiated Skin . . . . .	57
E. Inhibition of Erythema and Local Hyperthermia . . . . .	58
I. UV-Induced Erythema . . . . .	58
1. Systemic Administration of Drugs . . . . .	58
2. Topically or Intradermally . . . . .	62
II. Tetrahydrofurfuryl Nicotinate (THFN) Erythema . . . . .	63
III. Other Erythemas . . . . .	63
IV. Local Hyperthermia . . . . .	63
F. Conclusion . . . . .	69
References . . . . .	70

## CHAPTER 21

**Oedema and Increased Vascular Permeability.** C. G. VAN ARMAN

A. General Principles of Assays . . . . .	75
I. Statistical Considerations in Assay Work . . . . .	79
1. Relationship of Dose to Effect . . . . .	79
2. Definition of ED <sub>50</sub> . . . . .	79
3. Confidence Limits . . . . .	79
4. Coefficient of Variation . . . . .	80
5. The <i>g</i> Value . . . . .	80
6. The Lambda Value, $\lambda$ . . . . .	80
7. Errors of Types I and II . . . . .	80

B. Methods for Producing and Measuring Oedema and Increased Vascular Permeability . . . . .	81
I. Oedemas of the Rat's Paw . . . . .	81
1. Measurement . . . . .	81
2. Agents Causing Paw Oedema; Characteristics of Oedemas Caused by Several Agents . . . . .	82
II. Increased Vascular Permeability . . . . .	86
III. Oedema in the Pleural Space . . . . .	86
C. Conclusion . . . . .	87
References . . . . .	88

## CHAPTER 22

**Short-Term Drug Control of Crystal-Induced Inflammation. D. J. MCCARTY.**  
With 4 Figures

A. Historical Aspects . . . . .	92
B. Mechanism of Crystal-Induced Inflammation . . . . .	93
I. Phagocytosis . . . . .	93
II. Membranolysis . . . . .	93
III. Inflammatory Mediators . . . . .	96
IV. Chemotactic Factors . . . . .	97
C. Experimental Models . . . . .	98
I. Animal . . . . .	98
II. Man . . . . .	102
D. Therapy of Acute Attacks of Gout and Pseudogout . . . . .	102
I. Gout . . . . .	102
II. Pseudogout . . . . .	102
E. Summary . . . . .	104
References . . . . .	104

## CHAPTER 23

**Experimental Models of Arthritis in Animals as Screening Tests for Drugs to Treat Arthritis in Man. M. E. J. BILLINGHAM and G. E. DAVIES. With 2 Figures**

A. Introduction . . . . .	108
B. Advantages and Disadvantages of Models of Arthritis—Comparison With Acute Models . . . . .	108
C. Adjuvant-Induced Arthritis . . . . .	109
I. First Observation. First Use as a Screen for Anti-Inflammatory/Antirheumatic Drugs . . . . .	110
II. Production . . . . .	112
1. Adjuvant . . . . .	112
2. Route of Injection . . . . .	114

3. Species Variation and Strain Variation . . . . .	114
4. Time Course of the Disease . . . . .	115
III. Aetiology . . . . .	116
1. Role of Lymphatic System . . . . .	116
2. Immunological Mechanisms . . . . .	116
3. Histology . . . . .	117
4. Lysosomal Enzymes . . . . .	118
IV. Assessment . . . . .	118
1. Physical Assessment—Gross Measurements . . . . .	119
2. Physiological/Functional Parameters . . . . .	120
3. Biochemical Parameters . . . . .	120
4. Period of Dosing of Compounds . . . . .	123
V. Effect of Drugs . . . . .	124
1. Non-Steroid Anti-Inflammatory Drugs . . . . .	124
2. Steroid Anti-Inflammatory Drugs . . . . .	125
3. Gold, Chloroquine, and Penicillamine . . . . .	125
4. Immunosuppressant Drugs . . . . .	127
5. Antilymphocytic Serum, Antigens . . . . .	127
6. Non-Specific Inhibition . . . . .	129
7. The Effect of Adjuvant Arthritis on Drugs . . . . .	130
D. Arthritis Produced by Intra-Articular Injection of Antigens and Antibodies . . . . .	131
E. Arthritis Produced by Intra-Articular Injection of Lysosome Labilisers . . . . .	133
F. Arthritis Induced by Infectious Agents . . . . .	134
E. Conclusions . . . . .	134
References . . . . .	135

## CHAPTER 24

### **Antagonism of Bradykinin Bronchoconstriction by Anti-Inflammatory Drugs.**

P. J. PIPER and J. R. VANE

A. Introduction . . . . .	145
B. Production of Kinins and Other Mediators of Anaphylaxis in the Lungs . . . . .	146
I. In vitro . . . . .	146
II. In vivo . . . . .	146
III. Release of Catecholamines in vivo . . . . .	146
C. Action of Bradykinin on Lung Function . . . . .	147
I. Bronchial Smooth Muscle in vitro and in vivo . . . . .	147
II. Pulmonary Circulation . . . . .	148
D. Release of Prostaglandins and Precursors From Lungs by Bradykinin . . . . .	148
E. Actions of Prostaglandins in the Lungs . . . . .	150
I. Bronchial Smooth Muscle . . . . .	150
F. Interaction of Bradykinin With Prostaglandins in the Lungs . . . . .	153
I. As a Mediator . . . . .	153
II. As a Potentiator . . . . .	153
III. As a Mediator of Vascular Leakage . . . . .	154

G. Metabolism of Kinins in the Pulmonary Circulation . . . . .	154
H. Inhibition of Bronchoconstriction by Anti-Inflammatory Acids . . . . .	155
I. In vivo and in vitro Studies . . . . .	155
II. Comparison With Other Bronchoconstrictor Agents . . . . .	156
I. Possible Actions and Interactions of Kinins and Prostaglandins in Asthma	157
J. Summary and Conclusions . . . . .	158
References . . . . .	158

## CHAPTER 25

### **Interference of Anti-Inflammatory Drugs With Hypotension. B. B. VARGAFTIG.** With 11 Figures

Introduction . . . . .	164
A. Interference of Non-Steroidal Anti-Inflammatory Drugs With Hypotensive Effects of Potential Inflammatory Mediators . . . . .	164
I. Kinin Peptides . . . . .	164
II. Prostaglandins . . . . .	165
B. Interference by Non-Steroidal Anti-Inflammatory Drugs With the Hypotensive Effects of Agents That Release Potential Inflammatory Mediators . . . . .	166
I. Proteolytic Enzymes . . . . .	166
1. Kininogenases . . . . .	167
2. Thrombin . . . . .	168
3. Other Proteolytic Enzymes . . . . .	169
II. Inhibition of Hypotension Due to Substances That Activate Plasma Kininogenase . . . . .	169
1. Carrageenin . . . . .	169
2. Other Activators of Plasma Kininogenase . . . . .	171
III. Phospholipase $A_2$ . . . . .	171
C. Interference of Anti-Inflammatory Drugs With Hypotensive Responses to Lipid Derivatives . . . . .	173
I. Effects of Arachidonic Acid on Arterial Blood Pressure . . . . .	174
1. Mechanism of Action of Arachidonic Acid on Blood Pressure . . . . .	174
II. Effects of Fatty Acids Other Than Prostaglandin Precursors . . . . .	180
III. Slow Reacting Substance C . . . . .	181
1. Mechanism of Action of Slow Reacting Substance C . . . . .	184
D. Interference of Non-Steroidal Anti-Inflammatory Agents With Effects of Miscellaneous Agents . . . . .	185
I. Adenosine Nucleotides . . . . .	185
II. Collagen . . . . .	186
III. Anaphylatoxin . . . . .	187
IV. Depressor Active Substance (DAS) . . . . .	187
V. Platelet Clumping Substance . . . . .	187
VI. Barium Sulphate and Other Particulate Materials . . . . .	187

E. Interference of Non-Steroidal Anti-Inflammatory Agents With Hypotension in Endotoxin Shock . . . . .	188
I. Dogs . . . . .	188
II. Cats . . . . .	188
III. Other Animal Species . . . . .	190
F. Mechanism of Action of Hypotensive Agents Liable to Inhibition by Non-Steroid Anti-Inflammatory Drugs . . . . .	190
I. Structure-Activity Correlations . . . . .	190
1. Thiol and Anti-Oxidant Compounds . . . . .	191
II. Stereospecificity . . . . .	192
III. Mechanism of Action of Hypotensive Agents Subject to Inhibition by Non-Steroidal Anti-Inflammatory Drugs . . . . .	194
1. Bradykinin . . . . .	194
2. Collagen . . . . .	194
3. Carrageenin . . . . .	195
4. Adenosine Nucleotides . . . . .	195
IV. Conclusions . . . . .	196
1. Relevance of Hypotensive Responses to Inflammation and to Study of Inflammatory Events . . . . .	196
2. Multisequential Activation and Acute Hypotensive Responses: Prospects of Research . . . . .	197
References . . . . .	198

## CHAPTER 26

### **Antagonism of Pain and Hyperalgesia.** R. VINEGAR, J. F. TRUAX, J. L. SELPH, and P. R. JOHNSTON. With 3 Figures

A. Introduction . . . . .	209
I. Terminology . . . . .	209
II. Historical Introduction to Analgesic Testing in Hyperalgesic Animals . . . . .	210
B. Non-Hyperalgesic Mild Analgesic Assays . . . . .	218
I. Stretching Tests . . . . .	218
C. Assessment of Mild Analgesia in Humans . . . . .	219
I. Clinical Avaluation of Mild Analgesic Agents . . . . .	219
D. Conclusion . . . . .	220
References . . . . .	221

## CHAPTER 27

### **Inhibition of Cell Migration in vivo and Granuloma Formation.** M. DI ROSA

A. General Introduction . . . . .	223
I. Mechanisms of Cell Migration . . . . .	223
II. The Sequence of Cell Migration . . . . .	225

III. Fate of Emigrated Cells . . . . .	225
1. Polymorphs . . . . .	225
2. Mononuclear Cells . . . . .	226
IV. Granuloma Formation and Evolution . . . . .	227
B. Models for Leucocyte Emigration in vivo . . . . .	228
I. Generalities . . . . .	228
II. Histological Method . . . . .	229
III. Cell Collection From Cavities . . . . .	229
1. Natural Cavities . . . . .	229
2. Artificial Cavities . . . . .	231
IV. Cell Collection From Early Granulomata . . . . .	232
V. Cell Labelling . . . . .	232
C. Models for Granuloma Formation in vivo . . . . .	233
I. Cotton-Pellet Granuloma . . . . .	233
II. Granuloma Pouch . . . . .	234
III. Carrageenin Granuloma . . . . .	235
IV. Plastic Ring Granuloma . . . . .	235
V. Filter Paper Granuloma . . . . .	235
D. Inhibition of Cell Migration in vivo . . . . .	236
I. Steroids . . . . .	236
1. Neutrophils . . . . .	236
2. Mononuclear Cells . . . . .	237
II. Non-Steroid Anti-Inflammatory Drugs . . . . .	238
III. Immunosuppressive Agents . . . . .	240
IV. Endogenous Substances . . . . .	241
E. Inhibition of Granuloma Formation . . . . .	242
I. Steroid Anti-Inflammatory Drugs . . . . .	242
II. Non-Steroid Anti-Inflammatory Drugs . . . . .	243
III. Immunosuppressive Agents . . . . .	243
IV. Endogenous Substances . . . . .	244
F. Conclusions . . . . .	244
References . . . . .	245

## CHAPTER 28

**Inhibition of Fever.** C. ROSENDORFF and C. J. WOOLF. With 3 Figures

A. Introduction . . . . .	255
B. Pathogenesis of Fever . . . . .	255
I. Exogenous and Endogenous Pyrogen . . . . .	255
II. Site of Action of Pyrogens . . . . .	256
III. Mechanism of Action of Pyrogens . . . . .	257
1. Change in Set-Point or Gain? . . . . .	257
2. Role of Prostaglandins . . . . .	257
3. Role of Monoamines and Cyclic-AMP . . . . .	258
4. Ionic Mechanisms in Fever . . . . .	259

C. Antipyretics . . . . .	259
I. Possible Sites of Action of Antipyretics . . . . .	260
1. Inactivation of Bacterial Pyrogen (Site I) . . . . .	261
2. Inhibition of Endogenous Pyrogen Production or Release (Site II) . . . . .	261
3. Inhibition of Endogenous Pyrogen Activity (Site III) . . . . .	262
4. Access of Endogenous Pyrogen to the Central Nervous System (Site IV) . . . . .	262
5. Hypothalamic Thermoregulatory Centres (Site V) . . . . .	262
6. Suppression of Heat Production (Site VI) . . . . .	262
II. Possible Mechanisms of Antipyretic Action . . . . .	264
1. Inhibition of Prostaglandin Synthesis/Release . . . . .	264
2. Competitive Antagonism Between Pyrogens and Antipyretics for a Receptor Site . . . . .	265
3. Alteration in the Activity of Neurones in the Hypothalamus . . . . .	266
III. Antipyresis . . . . .	271
D. Inhibition of Fever by Other Means . . . . .	271
I. Increased Heat Loss . . . . .	271
II. Monoamine Blockade and Depletion . . . . .	272
III. Cholinergic Blockade . . . . .	272
E. Conclusion . . . . .	272
References . . . . .	274

## CHAPTER 29

### **Evaluation of the Toxicity of Anti-Inflammatory Drugs.** P. W. DODGE, D. BRODIE, and B. D. MITCHELL

A. Introduction . . . . .	280
I. Historical Overview . . . . .	280
B. Evaluation of Toxicity in Man . . . . .	281
I. Gastrointestinal Tract . . . . .	282
II. Central Nervous System . . . . .	283
III. Dermatological Disorders . . . . .	283
IV. Haematopoietic System . . . . .	283
V. Ocular Disturbances . . . . .	284
VI. Renal Side Effects . . . . .	284
VII. Miscellaneous Side Effects . . . . .	284
C. Methods Used to Evaluate Toxicity in Animals . . . . .	284
I. Gastrointestinal . . . . .	285
II. Kidney . . . . .	286
III. Haematopoietic System . . . . .	287
IV. Liver . . . . .	287
V. Skin . . . . .	288
VI. Eye . . . . .	289
VII. Central Nervous System . . . . .	289



D. Correlation of Experimental Models With Clinical Toxicity . . . . .	289
I. Non-Steroid Anti-Inflammatory Drugs . . . . .	289
1. Salicylates . . . . .	289
2. Indomethacin . . . . .	292
3. Phenylbutazone . . . . .	293
4. Arylalkanoic Acids . . . . .	293
5. Gold . . . . .	294
II. Steroids . . . . .	294
E. Summary . . . . .	295
References . . . . .	296

## Pharmacology of the Anti-Inflammatory Agents

### CHAPTER 30

#### Prostaglandin Synthetase Inhibitors I. T. Y. SHEN. With 1 Figure

A. Introduction . . . . .	305
B. Inhibition of Synthetase by Substrate Analogues and Fatty Acid Derivatives . . . . .	308
I. Unsaturated Fatty Acids . . . . .	308
II. Bicyclic Analogues . . . . .	310
C. Regulation of Enzymic Factors: Co-Factors, Stimulation, and Catabolism . . . . .	310
I. Regulation of Biosynthesis . . . . .	310
II. Catabolic Enzymes . . . . .	313
D. Inhibition by Non-Steroid Anti-Inflammatory Agents . . . . .	313
I. An Overview of Structure-Activity Relationship . . . . .	313
1. Correlation of PG Synthetase Inhibition With Anti-Inflammatory Action . . . . .	313
2. General Structure-Activity Relationship . . . . .	315
II. Salicylates . . . . .	316
III. Indomethacin, Sulindac, and Congeners . . . . .	317
IV. Substituted Aryl Aliphatic Acids . . . . .	321
V. Fenamates . . . . .	323
VI. Other Acidic Anti-Inflammatory Agents . . . . .	325
VII. Non-Acidic Anti-Inflammatory Agents . . . . .	327
E. Effects of Corticosteroids . . . . .	329
F. Inhibition and Stimulation by Other Pharmacological Agents . . . . .	329
I. Anti-Arthritic and Related Compounds . . . . .	329
II. Psychotropic Drugs . . . . .	331
III. Sulphydryl Reagents and Derivatives . . . . .	332
IV. Hormones and Mediators . . . . .	333
V. Inactive Pharmacological Agents . . . . .	334
G. The Search for New Inhibitors . . . . .	335
I. Current Research Trend . . . . .	335
II. Biochemical and Physiological Specificity . . . . .	336
III. Pharmacodynamic and Metabolic Control . . . . .	337

IV. Multiple-Action Inhibitors . . . . .	338
V. Synthetic and Physicochemical Approaches . . . . .	339
H. Pharmacokinetics of Prostaglandin Synthetase Inhibitors . . . . .	340
I. Conclusion . . . . .	341
References . . . . .	342

## CHAPTER 31

**Mode of Action of Anti-Inflammatory Agents Which are Prostaglandin Synthetase Inhibitors.** S. H. FERREIRA and J. R. VANE. With 2 Figures

A. Mediators and Inflammatory Responses . . . . .	348
B. Mechanism of Anti-Inflammatory Action . . . . .	351
I. Action on Step 1: Diminution of the Capability of Tissue Cells to Respond to Inflammatory Mediators . . . . .	352
1. Increased Dilatation and Vascular Permeability . . . . .	353
2. Pain and Hyperalgesia . . . . .	354
3. Increased Fibroblast Proliferation and Secretion . . . . .	354
II. Action on Step 2: Pharmacological Receptor Antagonism . . . . .	355
III. Action on Step 3: Inhibition of Extracellular Enzymic Activities Which Generate Inflammatory Mediators or Cause Injury to Cell Membranes and/or Tissue Components . . . . .	356
IV. Action on Step 4: Inhibition of the Release of Intracellular Lytic Enzymes or Mediator-Genases or Stored Receptor-Mediators . . . . .	358
V. Action on Step 5: Inhibition of the Synthesis of Inflammatory Mediators . . . . .	360
1. Prostaglandin Synthesis and Release . . . . .	361
2. Prostaglandins and Inflammatory Signs and Symptoms . . . . .	363
3. Correlation Between in vitro Inhibition of Prostaglandin Synthesis and Anti-Inflammatory Activity . . . . .	368
4. Inhibition of Prostaglandin Synthesis in vivo and Inflammatory Signs and Symptoms . . . . .	370
VI. Action on Step 6: Inhibition of Cell Migration . . . . .	374
VII. Action on Step 7: Inhibition of the Generation of the Effective Inflammatory Trauma . . . . .	375
C. Side-Effects of Anti-Inflammatory Drugs Which are Prostaglandin Synthetase Inhibitors . . . . .	376
D. Theories and Theories . . . . .	379
References . . . . .	383

## CHAPTER 32

**Penicillamine and Drugs With a Specific Action in Rheumatoid Arthritis.**

E. C. HUSKISSON. With 8 Figures

A. Classification of Antirheumatic Drugs . . . . .	399
B. Penicillamine . . . . .	400
I. Actions in Man . . . . .	400
II. Possible Mode of Action and Effects in Animal Models . . . . .	404

C. Gold Salts . . . . .	405
D. Chloroquine and Other Antimalarials . . . . .	406
E. Levamisole . . . . .	407
F. Other Imidazole Derivatives . . . . .	409
G. Immunosuppressives . . . . .	410
H. Alclofenac . . . . .	410
I. Steroids . . . . .	411
J. Summary . . . . .	411
References . . . . .	412

## CHAPTER 33

**Antagonists of Histamine, 5-Hydroxytryptamine and SRS—A. A. F. GREEN,  
L. G. GARLAND, and H. F. HODSON. With 11 Figures**

A. Classification of Antihistamines . . . . .	415
B. Histamine H <sub>1</sub> Antagonists: Structure-Activity Relationships . . . . .	415
C. Histamine H <sub>1</sub> Antagonists: Inhibition of Responses to Histamine Involved in Inflammatory and Anaphylactic Reactions . . . . .	419
I. Guinea Pig . . . . .	421
II. Rat . . . . .	421
III. Rabbit . . . . .	422
IV. Mouse . . . . .	422
V. Man . . . . .	422
D. Histamine H <sub>2</sub> Antagonists: Chemical Considerations . . . . .	423
E. Inhibition of Cardiovascular Responses to Histamine by H <sub>1</sub> and H <sub>2</sub> Antagonists . . . . .	424
F. Chemical and Pharmacological Classes of 5-Hydroxytryptamine Antagonists . . . . .	426
I. Chemical Classes . . . . .	426
II. "M" and "D" Receptors . . . . .	426
III. "Musculotropic" and "Neurotropic" Receptors . . . . .	427
G. Antagonists of 5-Hydroxytryptamine: Inhibition of Responses to 5-HT Involved in Inflammatory and Anaphylactic Reactions . . . . .	429
I. Guinea Pig . . . . .	429
II. Rat . . . . .	429
III. Rabbit . . . . .	432
IV. Mouse . . . . .	432
V. Man . . . . .	432
H. Effects of Antagonists of Histamine (H <sub>1</sub> Receptors) and 5-HT in Various Types of Inflammation . . . . .	432
I. Guinea Pig . . . . .	434
1. Thermal and Ultraviolet Injury . . . . .	434
2. Local Anaphylaxis . . . . .	436
3. Systemic Anaphylaxis . . . . .	437
4. Compound 48/80 and Polymyxin B . . . . .	439
5. Bradykinin . . . . .	439

II. Rat . . . . .	439
1. Thermal and Ultraviolet Injury . . . . .	439
2. Local Anaphylaxis . . . . .	441
3. Systemic Anaphylaxis . . . . .	443
4. Compound 48/80, Polymyxin, Dextran, and Egg White . . . . .	444
5. Turpentine Pleurisy . . . . .	445
6. Carrageenin Oedema . . . . .	446
7. Croton Oil . . . . .	447
8. Bradykinin . . . . .	447
III. Rabbit . . . . .	447
1. Thermal Injury . . . . .	447
2. Anaphylactic Reactions . . . . .	447
3. Inflammation Associated With Bacterial Infections . . . . .	448
IV. Mouse . . . . .	448
1. General Anaphylaxis . . . . .	448
2. Cutaneous Anaphylaxis . . . . .	449
3. Other Local Inflammatory Reactions . . . . .	450
4. Systemic Reactions Involving Inflammation . . . . .	450
V. Man . . . . .	451
1. Burns . . . . .	451
2. Compound 48/80 and Polymyxin . . . . .	451
3. Hypersensitivity States . . . . .	451
4. Rheumatoid Arthritis and 5-HT Antagonists . . . . .	451
VI. Bovine Anaphylaxis . . . . .	452
I. Antagonists of SRS-A . . . . .	452
I. Non-Steroid Anti-Inflammatory Drugs . . . . .	453
II. Polyphlorethin Phosphate (PPP) . . . . .	454
III. FPL 55712 . . . . .	454
IV. Hydratropic Acids . . . . .	455
J. Prospects for New Drugs . . . . .	456
References . . . . .	457

## CHAPTER 34

**Inhibitors of the Release of Anaphylatic Mediators.** L. G. GARLAND, A. F. GREEN,  
and H. F. HODSON. With 26 Figures

A. Characteristics of Anti-Allergic Agents Discussed . . . . .	467
B. Cromoglycate and Similar Compounds . . . . .	467
I. Identification and Screening . . . . .	467
1. The Passive Cutaneous Anaphylaxis Reaction (PCA) in Rats . . . . .	468
2. Lung Anaphylaxis in vivo . . . . .	471
3. Passive Peritoneal Anaphylaxis . . . . .	472
4. Human Tissues in vitro . . . . .	474
5. Rat Tissues in vitro . . . . .	477

II. Structure-Activity Relationships . . . . .	478
III. Anti-Allergic Properties . . . . .	488
1. Tissue and Species Selectivity . . . . .	488
2. Inhibition of Mast Cell Reactions Provoked by Stimuli Other Than Antigen-Antibody Interactions . . . . .	497
3. Time Course Studies . . . . .	500
4. Tachyphylaxis . . . . .	504
IV. Studies of the Mechanism of Anti-Allergic Action . . . . .	506
V. Other Pharmacological Effects . . . . .	511
VI. Pharmacokinetics . . . . .	511
C. Other Inhibitors of Mediator Release . . . . .	512
I. Isosteres of Theophylline . . . . .	512
1. Structure-Activity Relationships . . . . .	512
2. Anti-Allergic Properties . . . . .	514
II. Antihistamines and Histamine . . . . .	515
III. Diethylcarbamazine . . . . .	517
1. Rat Peritoneal Cells in vivo . . . . .	517
2. Lung Tissue . . . . .	518
3. Human Leucocytes . . . . .	519
4. Passive Cutaneous Anaphylaxis Reactions . . . . .	519
IV. Chlorphenesin . . . . .	519
D. Prospects for New Drugs . . . . .	520
References . . . . .	520

## CHAPTER 35

**Cytostats With Effects in Chronic Inflammation.** K. BRUNE and M. W. WHITEHOUSE.  
With 1 Figure

A. Introduction . . . . .	531
B. General Pharmacology of Cytostats Effective in Chronic Inflammation . . . . .	534
I. „Immunosuppressants“ . . . . .	537
1. Alkylating Agents . . . . .	540
2. Anti-Metabolites . . . . .	545
II. Microtubular Inhibitors . . . . .	547
1. Colchicine . . . . .	548
C. Some Properties of Selected Compounds . . . . .	552
I. Microtubular Inhibitors . . . . .	552
1. Cytostatic Effects of Colchicine . . . . .	552
II. Cyclophosphamide . . . . .	553
1. Metabolism . . . . .	553
2. Properties of Some Metabolites . . . . .	558
3. Site of Action . . . . .	559
4. Some Side-Effects . . . . .	560

III. Chlorambucil . . . . .	561
1. Metabolism . . . . .	561
2. Anti-Inflammatory Effects . . . . .	561
3. Mode of Action . . . . .	561
IV. Methotrexate . . . . .	562
V. Azathioprine . . . . .	563
D. Current Problems . . . . .	564
Appendix. Synovectomy and Destruction of Pannus . . . . .	565
References . . . . .	566
Addendum . . . . .	577

## CHAPTER 36

**Control of Hyperuricemia.** J. KOVARSKY and E. W. HOLMES. With 2 Figures

A. Introduction . . . . .	579
B. Uric Acid Metabolism . . . . .	579
C. Biochemical Pharmacology of Hypouricemic Drugs . . . . .	581
I. Drugs Reducing Uric Acid Synthesis . . . . .	581
1. Allopurinol and Oxipurinol . . . . .	581
2. Thiopurinol . . . . .	583
3. Other Inhibitors of Uric Acid Synthesis . . . . .	584
II. Uricosuric Agents . . . . .	584
III. Uricolytic Agents . . . . .	587
D. Clinical Use of Hypouricemic Drugs . . . . .	587
I. Criteria for Selecting a Hypouricemic Drug . . . . .	587
II. Use of Individual Hypouricemic Drugs . . . . .	588
III. Toxicity of Hypouricemic Agents . . . . .	589
References . . . . .	590

## CHAPTER 37

**Anti-Inflammatory Steroids: Mode of Action in Rheumatoid Arthritis and Homograft Reaction.** M. K. JASANI. With 19 Figures

A. General Considerations . . . . .	598
B. Scope of the Review . . . . .	600
C. Naturally Occurring Anti-Inflammatory Steroids . . . . .	602
D. Synthetic Anti-Inflammatory Steroids . . . . .	604
E. Biological Activities Observed With Physiological Amounts of Cortisol-Like Steroids . . . . .	604
I. Metabolic Effects . . . . .	606
1. Gluconeogenesis . . . . .	606
2. Protein Metabolism . . . . .	606
3. DNA Synthesis . . . . .	607
4. Molecular Basis for Metabolic Effects . . . . .	608
5. Onset and Duration of Cortisol Action . . . . .	609

6. Mechanism of Action of Cortisol . . . . .	609
7. Glycogenolysis . . . . .	610
8. Lipolysis . . . . .	610
9. Relationship to Anti-Inflammatory, Anti-Allergic and Anti-Rheumatic Action . . . . .	611
10. Relationship to Clinically Undesirable Effects . . . . .	613
11. Implications for the Future . . . . .	614
II. Sodium Retaining Activity . . . . .	615
III. Control of Adrenocorticotrophic Hormone (ACTH) Synthesis and Secretion . . . . .	617
1. Neuroendocrine Control . . . . .	618
2. Negative Feedback Control . . . . .	619
3. Basis for Negative Feedback Control . . . . .	620
4. Role of Cytoplasmic Steroid Receptors . . . . .	620
5. Relationship to Clinically Desirable Effects . . . . .	620
6. Relationship to Clinically Undesirable Effects . . . . .	621
IV. Cardiovascular Effects . . . . .	622
1. Heart and Peripheral Blood Vessels in Adrenalectomised State . . . . .	622
2. Microcirculation . . . . .	622
3. Relationship to Anti-Inflammatory, Anti-Allergic, and Anti-Rheumatic Action . . . . .	626
4. Relationship to Clinically Undesirable Effects . . . . .	629
5. Pharmacological Implications . . . . .	633
F. Mode of Action in Homograft Reaction . . . . .	634
I. Interference With the Development of Circulating Sensitized Lymphocytes . . . . .	639
II. Effectiveness Against Inflammation Due to Locally Sensitized Lymphocytes . . . . .	641
III. Effectiveness Against Inflammation Due to Circulating Sensitized Lymphocytes . . . . .	642
IV. Clinical Relevance of Experimental Observations . . . . .	645
V. Relevance to Evaluation of More Effective Anti-Rejection and Anti-Rheumatic Drugs . . . . .	646
G. Concluding Remarks . . . . .	647
References . . . . .	648

## CHAPTER 38

**Anti-Inflammatory Agents of Animal Origin. M. J. H. SMITH and A. W. FORD-HUTCHINSON**

A. Introduction . . . . .	661
B. Definition and Evaluation of Anti-Inflammatory Activity . . . . .	661
C. Mechanisms of Action . . . . .	663
D. Individual Agents . . . . .	666
I. Alkoxyglycerols . . . . .	666
II. N(2-hydroxyethyl) Palmitamide . . . . .	667

III. Vitamins . . . . .	668
IV. Amino Acids . . . . .	669
V. Peptides . . . . .	669
1. Peptide 401 . . . . .	669
2. Rabbit Skin Protease Inhibitor . . . . .	671
3. Aprotinin (Trasylol) . . . . .	671
VI. Proteins . . . . .	672
1. Exogenous Enzymes . . . . .	672
2. Orgotein . . . . .	673
3. Inflamed Tissue Factors . . . . .	675
4. Antileucotactic Agents . . . . .	677
5. Antiproliferative Agents . . . . .	680
6. Antilymphocytic Serum . . . . .	681
VII. Tissue Hydrolysates . . . . .	682
1. Catrix . . . . .	682
2. Livingston Lysate . . . . .	683
3. Lysoartrosi . . . . .	683
VIII. Human Plasma Factor . . . . .	684
IX. Prostaglandins . . . . .	686
E. Summary and Conclusions . . . . .	687
References . . . . .	688

## CHAPTER 39

**Anti-Inflammatory Substances of Plant Origin. M. GÁBOR**

A. Introduction . . . . .	698
B. Anti-Inflammatory Action of Phenylbenzo- $\gamma$ -Pyrone (Flavone) Derivatives . . . . .	698
I. The Occurrence of Flavonoid Compounds in Nature . . . . .	698
II. The Chemistry of Flavonoid Compounds . . . . .	698
III. The Anti-Inflammatory Action of Flavonoids . . . . .	701
1. Influence on Mouse and Rat Paw Oedema . . . . .	701
2. Generalized Dextran Oedema in Rats . . . . .	705
3. Generalized Phospholipase Oedema in Rats . . . . .	705
4. Effect on the Development of the Granuloma Pouch . . . . .	706
5. Inflammation Caused by Cotton Pellet . . . . .	706
6. Erythema Produced by UV Radiation . . . . .	707
7. Inflammation Produced by Mustard Oil . . . . .	708
8. Influence on the Permeability-Increasing Action of Inflammatory Exudate . . . . .	708
9. Influence on the Inflammation Produced by Red Paprika (Capsicum annum L. Solanaceae) . . . . .	709
10. Effect of Citrus Flavonoid Complex on Experimentally Induced Mucous Membrane Inflammation . . . . .	709
11. Influence on Experimentally Induced Thrombophlebitis . . . . .	710
12. Allergic and Hyperimmune Inflammation of the Skin and Joints . . . . .	711



13. Data on the Mechanism of the Anti-Inflammatory Effect of  
    Flavonoids . . . . . 711

14. Discussion . . . . . 718

C. Anti-Inflammatory Activity of Natural Plant Coumarins (Benzo- $\alpha$ -Pyrones) 720

D. Anti-Inflammatory Activity of Natural Plant Triterpenoids . . . . . 723

    I. Escin . . . . . 723

    II. Gycyrrhetic Acid . . . . . 724

    III. Other Triterpenoids . . . . . 725

E. Colchicine . . . . . 725

F. Essential Components of Camomile . . . . . 726

    I. The Azulenes . . . . . 726

    II. (–)- $\alpha$ -Bisabolol . . . . . 728

    III. EN—IN—Dicycloether . . . . . 729

    IV. Flavonoids . . . . . 729

G. Miscellaneous . . . . . 729

References . . . . . 730

CHAPTER 40

**A Critical Comparison of the Evaluation of Anti-Inflammatory Therapy in Animal Models and Man.** P. J. L. HOLT. With 1 Figure

A. Introduction . . . . . 740

B. Comparison of Models of Inflammation With the Human Situation . . . 742

C. Analysis of Parameters of Inflammation in Man . . . . . 744

    I. Stiffness . . . . . 746

    II. Pain . . . . . 746

    III. Joint Tenderness . . . . . 747

    IV. Grip Strength . . . . . 747

    V. Joint Size . . . . . 748

    VI. Blood Flow and Vascular Permeability . . . . . 748

    VII. Radiographic Changes . . . . . 749

    VIII. Tests of Functional Ability . . . . . 750

    IX. Laboratory Assessment of Disease Activity . . . . . 750

D. Clinical Trials . . . . . 751

    I. Objectives . . . . . 752

        1. Improvement of Therapeutic Methods at Present Available . . 752

        2. Optimum Benefit in a Patient . . . . . 752

        3. Improvement of Methods of Monitoring Inflammation in Patients 752

        4. Development of New Human Models for the Evaluation of Drugs 752

        5. Discovery of New Therapeutic Agents . . . . . 753

        6. Promotion of Scientific Management of Disease . . . . . 753

    II. Assessment . . . . . 754

    III. Patient Selection . . . . . 755

    IV. Placebo Response . . . . . 757

    V. Conclusions . . . . . 758

E. Treatment	758
I. Rest	759
II. Heat	759
III. Exercise	759
IV. Anti-Inflammatory Therapy	760
1. Non-Steroid Anti-Inflammatory Drugs	760
2. Gold, Penicillamine, and Chloroquine	761
3. Corticosteroids	763
4. Cytotoxic (Immunosuppressant) Therapy	763
5. Local Anti-Inflammatory Therapy	763
6. Lymphocyte Depletion	764
7. Immune Potentiation	764
8. Removal of Antibody	764
9. X-Ray Irradiation	764
F. Summary	764
References	765
 Author Index	 767
 Subject Index	 863