

# Contents

## Part I. Molecular Biology and Biochemistry of Microbial Iron Transport

1. Comparative Biochemistry of Microbial Iron Assimilation .....	3
<i>Joe B. Neilands, Krystyna Konopka, Bernhard Schwyn, Mark Coy,     Ralph T. Francis, Barry H. Paw, and Anne Bagg</i>	
1.1. Introduction .....	
1.1.1. The Literature of Microbial Iron Metabolism .....	3
1.1.2. Rationale of the Comparative Approach .....	3
1.1.3. Iron in the Microbial Environment .....	5
1.1.4. Iron: Nutritious and Noxious .....	5
1.1.5. Siderophore vs. Non-Siderophore Iron Assimilation .....	6
1.2. Bacteria .....	7
1.2.1. <i>Escherichia coli</i> .....	7
1.2.1.1. The Aerobactin Operon of pColV-K30 .....	7
1.2.1.2. Regulation .....	10
1.2.1.3. Hemin as Iron Source .....	11
1.2.1.4. Siderophore-Mediated Utilization of Ovo- and Lacto-Transferrin Iron .....	13
1.2.2. <i>Rhizobium meliloti</i> .....	24
1.3. Fungi .....	24
1.3.1. Is there a Siderophore in Common Yeast? .....	25
1.3.2. Purification of $N^{\delta}$ -Hydroxyornithine: Acetyl CoA $N^{\delta}$ -Transacetylase from <i>Rhodotorula pilimanae</i> .....	26
1.4. Summary .....	28
References .....	30
2. Iron Transport Systems in <i>Escherichia coli</i> .....	35
<i>Volkmar Braun, Klaus Hantke, Katrin Eick-Helmerich, Wolfgang Köster,     Uwe Preßler, Martin Sauer, Sven Schäffer, Harald Schöffler, Horst Staudenmaier, and     Luitgard Zimmermann</i>	
2.1. Introduction .....	35
2.2. Genetics and Biochemistry of Aerobactin Biosynthesis .....	35
2.3. Chromosomal Genes for Ferric-Hydroxamate Uptake .....	37
2.3.1. FhuA (TonA) Receptor Protein in the Outer Membrane .....	37
2.3.2. The FhuC, D, and B Transport Proteins .....	39
2.3.3. Unusual Specificities for Ferric-Hydroxamate Uptake .....	41
2.4. The Iron-Dicitrate Transport System .....	41
2.5. Central Control of Iron-Regulated Systems .....	42

2.6. New Iron-Regulated Genes . . . . .	44
2.6.1. <i>fhuF</i> Locus . . . . .	44
2.6.2. <i>fis</i> Locus . . . . .	44
2.6.3. <i>irrA</i> Locus . . . . .	45
2.6.4. <i>cirB</i> Locus . . . . .	45
2.7. Regulation of the Activity of Outer Membrane Receptor Proteins . . . . .	45
2.7.1. FhuE Consensus Sequence . . . . .	46
2.7.2. Further Homologies between Outer Membrane Receptor Proteins. Consensus Sequences in the TonB Protein . . . . .	46
2.7.3. The ExbB Protein . . . . .	47
2.8. Perspectives . . . . .	47
References . . . . .	50
<b>3. Plasmid-Mediated Iron Transport in Pathogenic Bacteria . . . . .</b>	<b>53</b>
<i>Jorge H. Crosa</i>	
3.1. Introduction . . . . .	53
3.2. Transposition Analysis of the Iron Uptake Region of pJM1 . . . . .	54
3.3. Definition of the pJM1 DNA Region Encoding the OM2 Outer Membrane Protein and Ferric Anguibactin Transport Activity . . . . .	56
3.4. Cloning of the Trans-Acting Factor Genes . . . . .	59
3.5. The Siderophore Anguibactin . . . . .	61
3.6. Flanking Sequences of the Aerobactin-Mediated Iron Uptake System . . . . .	62
References . . . . .	64
<b>4. Ferrienterobactin Transport in <i>Escherichia coli</i> . . . . .</b>	<b>67</b>
<i>Charles F. Earhart</i>	
4.1. Introduction . . . . .	67
4.2. Biosynthesis of Enterobactin . . . . .	70
4.2.1. Enzymology of Enterobactin Synthesis . . . . .	70
4.2.2. Molecular Genetic Studies of <i>ent</i> Genes . . . . .	71
4.3. Transport of Ferrienterobactin into the Cytoplasm . . . . .	72
4.3.1. Transport Proteins . . . . .	73
4.3.1.1. FepA . . . . .	73
4.3.1.2. FepB . . . . .	74
4.3.1.3. FepC . . . . .	75
4.3.1.4. Other Possible <i>fep</i> Genes . . . . .	75
4.3.1.5. TonB . . . . .	75
4.3.1.6. ExbB . . . . .	76
4.3.2. Release of Iron from Enterobactin . . . . .	77
4.3.3. Energy Requirements for Ferrienterobactin Transport . . . . .	78
4.4. Regulation of the Enterobactin System . . . . .	78
4.4.1. The <i>fur</i> Gene, Evidence for an Iron Regulon . . . . .	79
4.4.2. Regulation of Enterobactin Biosynthesis . . . . .	79
4.4.3. Regulation of <i>fepA</i> . . . . .	80

4.4.4. Some Possible Indirect Control Mechanisms .....	80
4.5. Concluding Remarks .....	81
References .....	81
<b>5. Sequences and Interactions of Proteins Participating in the Transport of Iron and Vitamin B<sub>12</sub> in <i>Escherichia coli</i> .....</b>	<b>85</b>
<i>Robert J. Kadner, Michael D. Lundrigan, and Knut Heller</i>	
5.1. Introduction .....	85
5.2. The Outer Membrane Receptors for Vitamin B <sub>12</sub> and Siderophore Complexes .....	86
5.2.1. Genetic Organization of the Receptors .....	86
5.2.2. Features of Predicted Receptors .....	86
5.2.3. Sequence Homologies .....	88
5.3. Transport of Vitamin B <sub>12</sub> across the Cytoplasmic Membrane .....	90
5.3.1. Role of the <i>btuCED</i> Region in Vitamin B <sub>12</sub> Transport .....	90
5.3.2. Products of the <i>btuCED</i> Region .....	92
5.3.3. Sequence of the <i>btuCED</i> Region and Properties of the Deduced Polypeptides .....	93
5.3.4. Consequences and Predictions .....	95
References .....	96
<b>6. Iron Transport in <i>Shigella</i> and <i>Vibrio</i> Species .....</b>	<b>99</b>
<i>Shelley M. Payne</i>	
6.1. Introduction .....	99
6.2. <i>Vibrio</i> Iron Transport Systems .....	100
6.3. <i>Shigella</i> Iron Transport Systems .....	103
6.4. <i>Shigella</i> Aerobactin Genes .....	103
6.5. Regulation of Aerobactin Synthesis in <i>Shigella</i> .....	105
6.6. Enterobactin Genes in <i>Shigella</i> .....	105
6.7. Iron Transport and Virulence of <i>Shigella</i> .....	107
6.8. Summary .....	108
References .....	109
<b>7. Iron, Siderophores, and Virulence in <i>Aeromonas hydrophila</i> .....</b>	<b>111</b>
<i>B. Rowe Byers</i>	
7.1. Introduction .....	111
7.2. The <i>Aeromonas hydrophila</i> Siderophore (AHS) .....	112
7.2.1. Isolation of AHS .....	112
7.2.2. Some Biological Properties of AHS .....	113
7.3. Experimental <i>Aeromonas hydrophila</i> Infections .....	113
7.4. AHS Vaccine and Anti-AHS Antibody Production .....	114
7.5. Initial Genetic Studies .....	114
7.6. Summary and Goals of the Research .....	115
References .....	116

<b>8. Biosynthesis of Aerobactin: Enzymological and Mechanistic Studies .....</b>	<b>117</b>
<i>Thammaiah Viswanatha, Edward W. Szczepan, and Gary J. Murray</i>	
8.1. Introduction .....	117
8.2. Factors Influencing <i>in vivo</i> Aerobactin Production .....	118
8.3. Studies with Cell-Free System .....	120
8.3.1. Lysine: $N^6$ -Hydroxylase ( $E_1$ ) .....	121
8.3.1.1. Preliminary Observations .....	121
8.3.1.2. Stability .....	121
8.3.1.3. Kinetic Properties .....	122
8.3.1.4. Influence of Glutamate and Analogs .....	123
8.3.2. Acetyl Transferase ( $E_2$ ) .....	126
8.3.3. Aerobactin Synthetase ( $E_3$ ) .....	126
8.4. Inter-Relationship between Pyruvate Metabolism and Aerobactin Production ..	128
8.5. Future Directions .....	131
<i>References</i> .....	132

## Part II. Chemistry and Mechanisms of Microbial Iron Transport

<b>9. The Crystal Structures, Conformations, and Configurations of Siderophores .....</b>	<b>135</b>
<i>Dick van der Helm, M.A.F. Jalal, and M.B. Hossain</i>	
9.1. Introduction .....	135
9.2. Catecholamides .....	135
9.3. Pseudobactins, Pyoverdins, Mycobactins .....	138
9.4. Ferrioxamines .....	142
9.5. Fusarinines .....	145
9.6. Coprogens .....	148
9.7. Ferrichromes .....	150
9.8. Iron Coordination and Model Complexes .....	155
9.8.1. Description .....	155
9.8.2. Models .....	156
9.8.3. Chelates of Siderophores .....	159
9.8.4. Specificity .....	162
9.9. Conclusions and Perspectives .....	162
<i>References</i> .....	163

<b>10. Bacterial Siderophores: Structure and Physicochemical Properties of Pyoverdins and Related Compounds .....</b>	<b>167</b>
<i>Pascal Demange, Salomé Wendenbaum, Andrew Bateman, Anne Dell, and Mohamed A. Abdallah</i>	
10.1. Introduction .....	167
10.2. The Pyoverdins of <i>Pseudomonas aeruginosa</i> ATCC 15692 .....	168
10.2.1. Isolation and Purification of the Pyoverdins of <i>Pseudomonas aeruginosa</i> ATCC 15692 .....	169
10.2.2. Physicochemical Properties of the Pyoverdins of <i>Pseudomonas aeruginosa</i> ATCC 15692 .....	169
10.2.3. Structure Elucidation of Pyoverdin Pa .....	170
10.2.3.1. NMR Spectra of Pyoverdin Pa .....	171
10.2.3.2. The Peptide Chain of Pyoverdin Pa .....	173
10.2.3.3. The Stereochemistry of the Different Chiral Groups of Pyoverdin Pa .....	174
10.2.4. The Structure of Pyoverdin Pa A, Pa B, and Pa C .....	176
10.3. The Structure of Azotobactin D, the Siderophore of <i>Azotobacter vinelandii</i> Strain D (CCM 289) .....	177
10.3.1. Isolation and Purification of Azotobactin .....	177
10.3.2. Physicochemical Properties of Azotobactin and Azotobactin $\alpha$ .....	177
10.3.3. Structure Elucidation of Azotobactin D .....	178
10.3.3.1. NMR Spectra of Azotobactin D .....	179
10.3.3.2. Determination of the Peptide Sequence .....	179
10.3.3.3. Stereochemistry of the Amino Acids and of the Chromophore of Azotobactin D .....	182
10.3.4. The Structure of Azotobactin $\alpha$ .....	184
10.4. General Structure of the Pyoverdins from Other Fluorescent Pseudomonads .....	184
References .....	186
<b>11. Siderophores of <i>Pseudomonas</i> – Biological Properties .....</b>	<b>189</b>
<i>Jean-Marie Meyer, Félix Hallé, Dany Hohnadel, Philippe Lemanceau, Harinirina Ratefiaravelo</i>	
11.1. Introduction .....	189
11.2. The Pyoverdines of Fluorescent Pseudomonads .....	189
11.2.1. The Fluorescent Pigment .....	189
11.2.2. Relationships between Pyoverdine and Iron .....	190
11.2.3. Strain Specificity of Pyoverdine .....	193
11.2.4. Ferrypyoverdine Reductase .....	195
11.2.5. Genetics of the Pyoverdine System .....	196
11.3. Siderophores Others than Pyoverdine .....	198
11.3.1. Fluorescent Pseudomonads .....	198
11.3.2. Non-Fluorescent Pseudomonads .....	198
11.4. Biological Interests of Pyoverdines .....	199
11.4.1. Siderophores and Human Pathogenicity of <i>P. aeruginosa</i> .....	199

11.4.2. Beneficial Effects of Plant Bacterization with Fluorescent Pseudomonads:	201
The Role of Pyoverdine .....	201
11.5. Conclusion .....	202
References .....	203
<b>12. Iron Metabolism in Mycobacteria .....</b>	<b>207</b>
<i>Colin Ratledge</i>	
12.1. Introduction .....	207
12.2. Consequences of Iron Deficiency in Mycobacteria .....	208
12.3. Mycobactin .....	208
12.3.1. Structure and Distribution .....	208
12.3.2. Function .....	210
12.3.3. Salicylate .....	214
12.3.4. Exochelins .....	215
12.4. Other Iron Uptake Systems .....	217
12.4.1. Citrate .....	218
12.4.2. Uptake from Other Siderophores .....	218
12.5. Conclusions .....	219
References .....	220
<b>13. Bacterial Iron Transport as a Target for Antibacterial Agents .....</b>	<b>223</b>
<i>Henry J. Rogers</i>	
13.1. Introduction .....	223
13.1.1. Bacterial Iron Transport as a Target for Inhibitors .....	223
13.2. Enterochelin .....	224
13.2.1. Effect of Serum on Iron Transport .....	224
13.3. Complexes of Enterochelin as Antibacterial Agents .....	225
13.3.1. Chemical Properties .....	225
13.3.2. Antibacterial Effects of Enterochelin Complexes .....	225
13.3.3. Mechanism of Action of $\text{Sc}^{3+}$ -enterochelin .....	226
13.3.3.1. General .....	226
13.3.3.2. Transport Studies .....	226
13.3.3.3. Metabolic Effects .....	227
13.3.4. Mechanism of Action of $\text{In}^{3+}$ -enterochelin .....	228
13.3.4.1. Structure of the Complex .....	228
13.3.4.2. Transport Studies .....	228
13.3.4.3. Metabolic Effects .....	229
13.4. Chelators from <i>Pseudomonas aeruginosa</i> .....	229
13.5. Aerobactin and Other Hydroxamates .....	229
13.6. Alboromycin .....	230
13.7. Future Prospects .....	230
References .....	231

<b>14. Reductive Mechanisms of Iron Assimilation . . . . .</b>	<b>235</b>
<i>Thomas Emery</i>	
14.1. Introduction . . . . .	235
14.2. Siderophore-Mediated Iron Transport . . . . .	235
14.2.1. Exchange . . . . .	236
14.2.2. Gallium Exchange . . . . .	237
14.2.3. Reductive Mechanisms . . . . .	238
14.3. Reductive Iron Uptake in Microorganisms . . . . .	238
14.4. Reductive Iron Uptake in Plants . . . . .	244
14.5. The Role of Reduction in Animal Iron Assimilation . . . . .	245
14.6. A Final Note . . . . .	248
References . . . . .	248
<b>15. Mössbauer Spectroscopy of Microbial Iron Uptake and Metabolism . . . . .</b>	<b>251</b>
<i>Berthold F. Matzanke</i>	
15.1. Introduction . . . . .	251
15.2. Microbial Iron Transport Agents . . . . .	251
15.3. Microbial Iron Storage Compounds . . . . .	261
15.4. Siderophore Uptake in Microorganisms and Iron Metabolism Monitored by <i>in vivo</i> Mössbauer Spectroscopy . . . . .	266
15.4.1. $^{57}\text{Fe}$ -Enterobactin Uptake in <i>Escherichia coli</i> . . . . .	267
15.4.2. Siderophore Transport in <i>Neurospora crassa</i> . . . . .	273
15.4.3. New Iron Metabolites and the <i>in vivo</i> Analysis of Enzymes. An Outlook . . . . .	278
References . . . . .	280
<b>16. Synthesis and Properties of Polyamine Catecholamide Chelators . . . . .</b>	<b>285</b>
<i>Raymond J. Bergeron</i>	
16.1. Introduction . . . . .	285
16.2. Polyamine Catecholamide Siderophores . . . . .	286
16.2.1. Synthetic Overview for Parabactin and Agrobactin Series . . . . .	286
16.2.2. Molecular Disconnection Analysis for Parabactin and Agrobactin Series . . . . .	287
16.3. Synthesis of Catecholamide Chelators . . . . .	288
16.3.1. Secondary <i>N</i> -Benzylated Triamines . . . . .	288
16.3.2. Synthesis of Bis- $N^1,N^8$ -(2,3-dihydroxybenzoyl)spermidine (Compound II) . . . . .	291
16.3.3. Synthesis of Parabactin Analogues . . . . .	292
16.3.4. A Biomimetic Synthesis of Parabactin Analogues . . . . .	293
16.3.5. Synthesis of Parabactin . . . . .	294
16.3.6. Synthesis of Parabactin Azide . . . . .	295
16.3.7. Synthesis of a Parabactin Affinity Column . . . . .	298
16.3.8. Synthesis of Agrobactin . . . . .	299

16.3.9.	<i>N</i> -Terminal Bis( <i>t</i> -butoxycarbonylated) Triamines; Reagents for Synthesis of Agrobactin A and Homologues; Disconnection Analysis . . . . .	300
16.3.10.	Synthesis of Agrobactin A . . . . .	302
16.3.11.	Triprotected Triamines; Reagents for the Synthesis of Vibriobactin; Disconnection Analysis . . . . .	302
16.3.12.	Synthesis of Vibriobactin . . . . .	305
16.4.	$^1\text{H}$ NMR of Catecholamide Chelators . . . . .	305
16.5.	Biological Properties of Polyamine Catecholamide Iron Chelators . . . . .	307
16.5.1.	Effects of Catecholamide Iron Chelators on Microbial Growth . . . . .	307
16.5.2.	Effects of Catecholamide Iron Chelators on the Growth of Tumor Cells . . . . .	311
	<i>References</i> . . . . .	314
17.	<b>Molecular Recognition and Transport of Siderophores in Fungi . . . . .</b>	317
	<i>Günther Winkelmann and Hans-Georg Huschka</i>	
17.1.	Introduction . . . . .	317
17.2.	Mutants of Desferrisiderophore Biosynthesis . . . . .	317
17.3.	Transport Mechanisms . . . . .	318
17.4.	Specificity of Transport . . . . .	319
17.5.	Siderophore Recognition . . . . .	321
17.6.	Uptake of Coprogens . . . . .	321
17.7.	Uptake of Ferrichromes . . . . .	322
17.8.	Position of <i>N</i> -Acyl Residues . . . . .	322
17.9.	Peptide Backbone . . . . .	324
17.10.	Semisynthetic Ferrichromes . . . . .	325
17.11.	Cyclic Nature of the Backbone . . . . .	325
17.12.	Configuration . . . . .	325
17.13.	Inhibition Studies . . . . .	327
17.14.	Effect of Temperature . . . . .	329
17.15.	The Driving Force . . . . .	330
	<i>References</i> . . . . .	335
	<b>Part III. Strategies for Iron Acquisition in Higher Plants . . . . .</b>	337
18.	<b>Biochemical Basis of Iron Efficiency Reactions in Plants . . . . .</b>	339
	<i>Frits Bienfait</i>	
18.1.	Dicotyledons and Non-Grass Monocotyledons . . . . .	339
18.1.1.	Increased Capacity to Reduce Ferric Chelates (Turbo Reductase) . . . . .	339
18.1.2.	Rhizosphere Acidification by Proton Extrusion . . . . .	344
18.1.3.	Excretion of Phenolic Compounds . . . . .	344
18.1.4.	Excretion of Flavins . . . . .	345
18.2.	Grasses . . . . .	345
18.3.	Regulation of Iron-Efficiency Responses . . . . .	346
	<i>References</i> . . . . .	349

<b>19. Existence of Two Different Strategies for the Acquisition of Iron in Higher Plants .....</b>	<b>353</b>
<i>Volker Römheld</i>	
19.1. Introduction .....	353
19.2. Mechanisms of Iron Acquisition .....	325
19.3. Phylogenetic Distribution of the Various Adaptive Mechanisms (Strategies) .....	355
19.4. Strategy I .....	359
19.4.1. Fe(III) Reduction .....	359
19.4.2. Proton Release .....	360
19.4.3. Cooperative System .....	362
19.5. Strategy II: Phytosiderophore System .....	363
19.5.1. Iron Mobilizing Root Exudates .....	362
19.5.2. Specific Membrane Transport System for Ferrated Phytosiderophores .....	364
19.6. Ecological Significance .....	367
19.7. Agricultural Significance .....	372
References .....	373
 <b>20. Microbial Siderophores as Iron Sources for Plants .....</b>	 375
<i>D. E. Crowley, C. P. P. Reid, and P. J. Szaniszlo</i>	
20.1. Introduction .....	375
20.2. Chemistry of Iron in Soils .....	375
20.3. Iron Chelation and Chelate Stability .....	376
20.4. Production and Occurrence of Siderophores in Soils .....	378
20.5. Plant Utilization of Chelated Iron .....	380
20.6. Summary .....	384
References .....	385
 <b>21. Plant Growth Stimulation by Biological Interference in Iron Metabolism in the Rhizosphere .....</b>	 387
<i>Letty A. de Weger, Bob Schippers, and Ben Lugtenberg</i>	
21.1. Biology of Yield Decrease Resulting from Short Rotation .....	387
21.1.1. Introduction .....	387
21.1.2. Suppression of Yield Decrease by Fluorescent <i>Pseudomonas</i> spp. ....	387
21.1.3. A Model to Explain Suppression of Yield Decrease by <i>Pseudomonas</i> Bacteria ...	388
21.1.3.1. Interference of Fluorescent <i>Pseudomonas</i> spp. with Iron Metabolism .....	388
21.1.3.2. Root Colonization .....	389
21.2. Molecular Aspects of Interference of <i>Pseudomonas</i> Bacteria with Iron Metabolism in the Soil .....	389
21.2.1. Antagonistic Activity of Fluorescent <i>Pseudomonas</i> spp. is the Result of Siderophores Produced during Limitation for Fe <sup>3+</sup> .....	390
21.2.2. Siderophores Produced by <i>Pseudomonas</i> spp. ....	390
21.2.3. Analysis of the Genes Involved in the Synthesis of Siderophores .....	392

21.2.4.	Uptake of Fe <sup>3+</sup> -Siderophore Complex . . . . .	392
21.2.5.	Iron Limitation in the Rhizosphere . . . . .	393
21.2.6.	Role of Siderophores in Plant Growth Stimulation . . . . .	394
21.2.7.	Beneficial <i>Pseudomonas</i> spp. Comprise a Strongly Diverse Family of Strains . . . . .	394
21.2.8.	Nature of Harmful Microorganisms . . . . .	395
21.3.	Importance of Plant-Root Colonization for Yield Increase . . . . .	395
21.3.1.	Rationale . . . . .	395
21.3.2.	Factors Influencing Plant-Root Colonization . . . . .	396
21.3.3.	Strategy for Studying Plant-Root Colonization . . . . .	396
21.4.	Application in the Field . . . . .	398
<i>References</i> . . . . .		398
<b>22.</b>	<b>Mugineic Acids, Studies on Phytosiderophores . . . . .</b>	<b>401</b>
<i>Kyosuke Nomoto, Yukio Sugiura, and Sei-ichi Takagi</i>		
22.1.	Introduction . . . . .	401
22.2.	Discovery of Mugineic Acids from Root Washings of Gramineous Plants (Rice and Oat) . . . . .	402
22.2.1.	Plant Culture and Collection of Root Washings . . . . .	402
22.2.2.	Determination of the Iron-Chelating Activity . . . . .	402
22.2.3.	Fractionation of the Root Washings . . . . .	403
22.2.4.	Iron-Solubilizing Capacity of Oat and Rice Root Washings . . . . .	403
22.3.	Isolation of Mugineic Acids . . . . .	404
22.4.	Structural Elucidation of Mugineic Acids . . . . .	404
22.4.1.	Mugineic Acid . . . . .	404
22.4.2.	Pseudo-Mugineic Acids . . . . .	408
22.4.3.	Related Amino Acids . . . . .	411
22.5.	Syntheses of Mugineic Acids . . . . .	411
22.5.1.	Syntheses of 2'-Deoxymugineic Acid and Avenic Acid A . . . . .	411
22.5.2.	Synthesis of Mugineic Acid . . . . .	412
22.6.	Physiological Aspects of Mugineic Acid . . . . .	412
22.6.1.	Diurnal Variation in Mugineic Acid Secretion by Iron-Stressed Barley Roots . . . . .	412
22.6.2.	Effects of Additional Iron(III) Ion on Fluctuation in Daily Mugineic Acid Secretion in Barley . . . . .	413
22.6.3.	Effect of Mugineic Acid and Its Related Compounds on <sup>59</sup> Fe-Uptake and Synthesis of Chlorophyll in Rice Plants . . . . .	414
22.7.	Molecular Structure and Properties of the Mugineic Acid-Fe(III) Complex . . . . .	415
22.7.1.	Molecular Structure . . . . .	415
22.7.2.	Spectroscopic and Electrochemical Properties of the Mugineic Acid-Fe(III) Complex . . . . .	417
22.7.3.	Potentiometric Titration . . . . .	420
22.8.	Solution Structures of Mugineic Acid and Its Metal Complexes . . . . .	420
22.9.	Inhibition Mechanism of the Iron-Solubilizing Action by the Presence of Divalent Metals . . . . .	422
22.10.	Probable Mechanism for Iron-Transport in Gramineous Plants . . . . .	423
<i>References</i> . . . . .		424

## Part IV. Iron Transport in Animals

<b>23. Iron Bioavailability .....</b>	<b>429</b>
<i>Manju B. Reddy, Mankulathu V. Chidambaram, and George W. Bates</i>	
23.1. Prevalence, Causes and Effects of Iron Deficiency .....	429
23.2. Iron Absorption: Physiological Factors .....	430
23.3. Iron Absorption: Dietary Factors .....	431
23.4. <i>In vitro</i> Studies of Food Iron Bioavailability .....	432
23.5. Recent Observations on the <i>in vitro</i> Digestive Chemistry of Pinto Bean Iron .....	435
23.5.1. Methodological Aspects .....	435
23.5.2. Results .....	435
23.5.3. Conclusions .....	442
References .....	443
<b>24. Ferritin and Bacterioferritin: Iron Sequestering Molecules from Man to Microbe .....</b>	<b>445</b>
<i>Pauline M. Harrison, Simon C. Andrews, Geoffrey C. Ford, John M.A. Smith, Amyra Treffry, and Janice L. White</i>	
24.1. Introduction .....	445
24.2. Iron-Cores in Ferritins and Bacterioferritins: Composition, Crystallinity, and Mössbauer Spectra .....	445
24.3. Haemosiderin in Vertebrates and Invertebrates .....	450
24.4. Three-Dimensional Structure of Apoferritin from Horse Spleen .....	452
24.5. Species Variation and Subunit Heterogeneity within Ferritins .....	456
24.5.1. Primary Structures of Mammalian and Amphibian Ferritins .....	456
24.5.2. Subunit Heterogeneity in Other Ferritins .....	459
24.5.3. Functional Significance of Subunit Heterogeneity .....	460
24.5.4. <i>In vitro</i> Iron Uptake Studies Relating to Heterogeneity .....	460
24.5.5. Heterogeneity Due to Post-Translational Effects .....	460
24.6. Molecular Mechanisms of Iron Sequestration by Ferritin .....	464
24.6.1. Role of the Protein .....	464
24.6.2. Location of Possible Fe(III) Ligands .....	465
24.6.3. Iron Entry into Ferritin Molecules .....	467
24.7. Bacterioferritins .....	469
24.7.1. The Structure of the Haemoprotein of Bacterioferritins .....	469
24.7.2. Functional Properties of Bacterioferritin .....	471
24.8. Mobilization of Ferritin Iron .....	471
24.9. Future Prospects .....	472
References .....	473

<b>25. The Role of Iron Binding Proteins in Bacterial Infections .....</b>	<b>477</b>
<i>Guenther Sawatzki</i>	
25.1. The Decrease of Plasma Iron in Infection .....	477
25.2. The Role of Iron-Saturation of Transferrin in Infection .....	477
25.3. Growth Inhibition of Microorganisms by Iron-Binding Proteins .....	479
25.4. Iron-Overload is a Risk Factor for Bacterial Infection .....	479
25.5. Lactoferrin, an Iron-Binding Protein Localized at Sites of Microbial Invasion .....	480
25.6. Lactoferrin in Neutrophil Granulocytes .....	480
25.7. Plasma Lactoferrin Levels after Bacterial Infection or LPS Challenge <i>in vivo</i> .....	481
25.8. The Role of Lactoferrin in Plasma Iron Decrease .....	482
25.9. Lactoferrin Can Capture Iron from Plasma Transferrin .....	483
25.10. The Course of Lactoferrin and Iron in Infection .....	485
25.11. The Cooperation of Iron, Transferrin, and Lactoferrin in Infection .....	487
References .....	488
<b>26. The Storage and Transport of Iron in Animal Cells .....</b>	<b>491</b>
<i>Elizabeth C. Theil and Philip Aisen</i>	
26.1. Introduction .....	491
26.2. Macromolecules of Iron Metabolism: Structure .....	491
26.2.1. Transferrin .....	491
26.2.2. The Transferrin Receptor .....	492
26.2.2.1. Occurrence .....	492
26.2.2.2. Structure .....	493
26.2.2.3. Ferritin .....	494
26.2.3.1. The Outer, Apoferritin Coat .....	494
26.2.3.2. The Iron/Protein Interface .....	495
26.2.3.3. The Inner, Iron Core and Hemosiderin .....	495
26.2.4. Ferritin Receptors .....	496
26.3. Macromolecules of Iron Metabolism: Synthesis .....	496
26.3.1. Transferrin .....	496
26.3.2. The Transferrin Receptor: Synthesis and Regulation .....	497
26.3.3. Ferritin .....	498
26.3.3.1. Apoferritin Synthesis .....	498
26.3.3.2. Formation of the Iron Core .....	499
26.4. Cellular Iron Metabolism .....	500
26.4.1. Iron Uptake .....	500
26.4.1.1. Introduction .....	500
26.4.1.2. Iron Uptake by Erythroid Cells .....	501
26.4.1.3. Transferrin Receptors and Iron Uptake in Non-Erythroid Cells .....	504
26.4.1.4. Alternative Views of Receptor-Transferrin Interactions .....	504
26.4.1.5. Are Transferrin and Its Receptor Essential for Physiological Uptake? .....	505
26.4.1.6. The Fate of the Transferrin Receptor .....	506
26.4.1.7. Acquisition of Iron from Sources Other than Transferrin .....	507
26.4.1.8. Other Routes for the Utilization of Transferrin-Bound Iron by Cells .....	508

26.4.2. Storage .....	508
26.4.2.1. Incorporation of Iron into Ferritin .....	509
26.4.2.2. Release of Iron from Ferritin .....	510
26.4.2.3. Advantages in Variable Rates of Storage Iron Turnover .....	511
26.4.3. Release of Iron from Cells .....	512
26.4.3.1. Iron Release by Hepatocytes .....	512
26.4.3.2. Iron Release by Reticuloendothelial Cells .....	513
26.5. Summary and Perspective .....	514
<i>References</i> .....	515
Index .....	521