DEDICATION

This book is dedicated to the memory of Igor Stojiljkovic, M.D., Ph.D., who passed away on 10 October 2003 after a heroic 2-year battle with cancer. Igor was one of the bright young stars in the fields of iron transport and bacterial infection. However, he was not just a highly creative and imaginative scientist but was, foremost, a first-class gentleman, a kind human being, and, for those of us who had the fortune of being close to him, an outstanding and warm friend, always ready to give positive advice and constructive criticism. He was an indefatigable worker—until not long before his untimely passing, Igor managed to write the first drafts and give directions for the completion of his contribution to this book, the two chapters that were finished by his postdoctoral fellows.

Igor received his M.D. and Ph.D. degrees from the University of Zagreb, Croatia, and carried out postdoctoral research at the University of Tübingen, Germany, and at the Oregon Health and Science University in Portland. He became a tenured Associate Professor at Emory University in 2002.

(Continues)
One of his major scientific interests was to understand how microorganisms obtain and use iron for their metabolic purposes. He focused on the ability of bacteria to assimilate heme, a ubiquitous source of iron. This research included identifying and characterizing bacterial components that are involved in the assimilation of heme (iron), understanding the mechanisms of function of heme assimilation systems, and studying genetic mechanisms causing the expression of these systems to vary. He also determined the virulence potential of these systems in different pathogens, the importance of these mechanisms for the population biology of pathogens, and novel approaches that would exploit heme assimilation as a target against pathogenic bacteria.

Igor's great joy for life and his incredible capacity to be imaginative and creative will always be remembered by all of us. We know that his scientific legacy will be perpetuated by those students and postdoctoral fellows who had the fortune of training with him.
CONTENTS

Contributors xi
Preface xvii

I. SIDEROPHORES AND HEMOPHORES: PROPERTIES AND BIOSYNTHESIS OF BACTERIAL IRON AND HEME CARRIERS 1

1. Biochemical and Physical Properties of Siderophores  
   Kenneth N. Raymond and Emily A. Dertz 3

2. Siderophore Biosynthesis in Bacteria  
   Christopher T. Walsh and C. Gary Marshall 18

3. Hemophore-Dependent Heme Acquisition Systems  
   Laurent Debarbieux and Cécile Wandersman 38

II. IRON TRANSPORT PROTEINS: STRUCTURAL STUDIES 49

4. Structure of Outer Membrane Receptor Proteins  
   Dick van der Helm 51

5. Bacterial Heme and Hemoprotein Receptors  
   Donna Perkins-Balding, Andrew Rasmussen, and Igor Stojiljkovic 66

6. Bacterial Heme Oxygenases  
   Melanie Ratliff-Griffin, Angela Wilks, and Igor Stojiljkovic 86
7. The TonB, ExbB, and ExbD Proteins
   Kathleen Postle and Ray A. Larsen
   96

8. Periplasmic Binding Proteins Involved in Bacterial Iron Uptake
   Karla D. Krewulak, R. Sean Peacock, and Hans J. Vogel
   113

III. IRON TRANSPORT, ENERGETICS, AND REGULATION IN ESCHERICHIA COLI K-12: A PROTOTYPE FOR IRON TRANSPORT SYSTEMS IN GRAM-NEGATIVE BACTERIA

9. Iron Uptake via the Enterobactin System
   Charles F. Earhart
   133

10. Transport Biochemistry of FepA
    Phillip E. Klebba
    147

11. Ferrichrome- and Citrate-Mediated Iron Transport
    Volkmar Braun, Michael Braun, and Helmut Killmann
    158

12. Ferrous Iron Transport
    Klaus Hantke
    178

13. Mode of Binding of the Fur Protein to Target DNA: Negative Regulation of Iron-Controlled Gene Expression
    Víctor de Lorenzo, José Perez-Martín, Lucía Escolar, Graziano Pesole, and Giovanni Bertoni
    185

IV. IRON TRANSPORT SYSTEMS IN PATHOGENIC BACTERIA

14. Pathogenic Escherichia coli, Shigella, and Salmonella
    Shelley M. Payne and Alexandra R. Mey
    199

15. Yersinia
    Robert D. Perry
    219

16. Vibrio
    Manuela Di Lorenzo, Michiel Stork, Alejandro F. Alice, Claudia S. López, and Jorge H. Crosa
    241

17. Neisseria
    Cynthia Nau Cornelissen and P. Frederick Sparling
    256
18. *Haemophilus*
Daniel J. Morton and Terrence L. Stull
273

19. *Pseudomonas*
Keith Poole
293

20. *Bordetella*
Timothy J. Brickman, Carin K. Vanderpool, and Sandra K. Armstrong
311

21. *Porphyromonas gingivalis*
Caroline Attardo Genco, Waltena Simpson, and Teresa Olczak
329

22. *Corynebacterium diphtheriae*
Michael P. Schmitt
344

23. *Pathogenic Mycobacteria*
G. Marcela Rodriguez and Issar Smith
360

24. *Legionella*
Nicholas P. Cianciotto
372

25. *Staphylococcus, Streptococcus, and Bacillus*
David E. Heinrichs, Andrea Rahn, Suzanne E. Dale, and Michael Tom Sebulsky
387

26. *Erwinia, a Plant Pathogen*
Dominique Expert, Lise Rauscher, and Thierry Franza
402

27. Therapeutic Uses of Iron(III) Chelators and Their Antimicrobial Conjugates
Vinay Girijavallabhan and Marvin J. Miller
413

V. **IRON TRANSPORT AND ECOLOGY** 435

28. Ecology of Siderophores
Günther Winkelmann
437

29. Environmental Fluorescent *Pseudomonas* and Pyoverdine Diversity: How Siderophores Could Help Microbiologists in Bacterial Identification and Taxonomy
Jean-Marie Meyer and Valérie A. Geoffroy
451

30. Mechanisms and Regulation of Iron Uptake in the Rhizobia
Andrew W. B. Johnston
469

Index 489
CONTRIBUTORS

Alejandro F. Alice
Department of Molecular Microbiology L220, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239

Sandra K. Armstrong
Department of Microbiology, University of Minnesota, MMC 196, 420 Delaware Street S.E., Minneapolis, MN 55455–0312

Giovanni Bertoni
Dipartimenti di Genetica e Fisiologia, via Celoria, 26, 20133 Milano, Italy

Michael Braun
Mikrobiologie/Membranphysiologie, Universität Tübingen, Auf der Morgenstelle 28, D–72076 Tübingen, Germany

Volkmar Braun
Mikrobiologie/Membranphysiologie, Universität Tübingen, Auf der Morgenstelle 28, D–72076 Tübingen, Germany

Timothy J. Brickman
Department of Microbiology, University of Minnesota, MMC 196, 420 Delaware Street S.E., Minneapolis, MN 55455–0312

Nicholas P. Cianciotto
Department of Microbiology and Immunology, Northwestern University Medical School, 320 East Superior St., Chicago, IL 60611

Cynthia Nau Cornelissen
Department of Microbiology and Immunology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298–0678

Jorge H. Crosa
Department of Molecular Microbiology L220, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239

Suzanne E. Dale
Department of Microbiology and Immunology, University of Western Ontario, London, Ontario N6A 5C1, Canada
Laurent Debarbieux  
Unité des Membranes Bactériennes, Institut Pasteur (CNRS URA 2172),  
25 rue du Dr. Roux, 75724 Paris Cedex 15, France

Victor de Lorenzo  
Centro Nacional de Biotecnología del CSIC, Campus Universidad Autónoma,  
Madrid 28043, Spain

Emily A. Dertz  
Department of Chemistry, University of California, Berkeley, CA 94720–1460

Manuela Di Lorenzo  
Department of Molecular Microbiology L220, Oregon Health and Science University,  
3181 SW Sam Jackson Park Road, Portland, OR, 97239

Charles F. Earhart  
Section of Molecular Genetics and Microbiology, The University of Texas at Austin,  
Austin, Texas 78712–1095

Lucía Escolar  
Centro Nacional de Biotecnología del CSIC, Campus Universidad Autónoma,  
Madrid 28043, Spain

Dominique Expert  
Laboratory of Plant Pathology, UMR 217 INRA/INA P-G, Université Paris 6,  
16 rue Claude Bernard, F-75005 Paris, France

Thierry Franza  
Laboratory of Plant Pathology, UMR 217 INRA/INA P-G, Université Paris 6,  
16 rue Claude Bernard, F-75005 Paris, France

Caroline Attardo Genco  
Department of Medicine, Section of Infectious Diseases, Boston University School of Medicine, Boston, MA 02118

Valérie A. Geoffroy  
Laboratoire de Microbiologie et Génétique, Université Louis-Pasteur–CNRS FRE 2326,  
F-67000 Strasbourg, France

Vinay Girijavallabhan  
Department of Chemistry and Biochemistry, 251 Nieuwland Science Center,  
University of Notre Dame, Notre Dame, IN 46556

Klaus Hantke  
Mikrobiologie/Membranphysiologie, Universität Tübingen, Auf der Morgenstelle 28,  
D-72076 Tübingen, Germany

David E. Heinrichs  
Department of Microbiology and Immunology, University of Western Ontario,  
London, Ontario N6A 5C1, Canada

Andrew W. B. Johnston  
School of Biological Sciences, University of East Anglia, Norwich NR4 7TJ,  
United Kingdom
Helmut Killmann
Mikrobiologie/Membranphysiologie, Universität Tübingen, Auf der Morgenstelle 28,
D-72076 Tübingen, Germany

Phillip E. Klebba
Department of Chemistry & Biochemistry, University of Oklahoma,
620 Parrington Oval, Norman, OK 73019

Karla D. Krewulak
Structural Biology Research Group, Department of Biological Sciences, University of
Calgary, Calgary, Alberta T2N 1N4, Canada

Ray A. Larsen
Department of Biological Science, Bowling Green State University,
Bowling Green, OH 43403–0212

Claudia S. López
Department of Molecular Microbiology L220, Oregon Health and Science University,
3181 SW Sam Jackson Park Road, Portland, OR 97239

C. Gary Marshall
Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School,
Boston, MA 02115

Alexandra R. Mey
Department of Molecular Genetics and Microbiology, The University of Texas at Austin,
Austin, TX 78712

Jean-Marie Meyer
Laboratoire de Microbiologie et Génétique, Université Louis-Pasteur—CNRS FRE 2326,
F-67000 Strasbourg, France

Marvin J. Miller
Department of Chemistry and Biochemistry, 251 Nieuwland Science Center,
University of Notre Dame, Notre Dame, IN 46556

Daniel J. Morton
Department of Pediatrics, University of Oklahoma Health Sciences Center,
Oklahoma City, OK 73104

Teresa Olczak
Institute of Biochemistry and Molecular Biology, Wroclaw University, Przybyszewskiego
63/77, 51–148 Wroclaw, Poland

Shelley M. Payne
Department of Molecular Genetics and Microbiology, The University of Texas at Austin,
Austin, TX 78712

R. Sean Peacock
Structural Biology Research Group, Department of Biological Sciences, University of Calgary,
Calgary, Alberta T2N 1N4, Canada
CONTRIBUTORS

José Perez-Martín
Centro Nacional de Biotecnología del CSIC, Campus Universidad Autónoma, Madrid 28043, Spain

Donna Perkins-Balding
Department of Microbiology and Immunology, Emory School of Medicine, Rollins Research Center, 1510 Clifton Rd., Rm. 3152, Atlanta, GA 30322

Robert D. Perry
Department of Microbiology, Immunology, and Molecular Genetics, MS415, Medical Center, University of Kentucky, Lexington, KY 40536–0298

Graziano Pesole
Dipartimenti di Genetica e Fisiologia, via Celoria, 26, 20133 Milano, Italy

Keith Poole
Department of Microbiology and Immunology, Queen’s University, Kingston, Ontario K7L 3N6, Canada

Kathleen Postle
School of Molecular Biosciences, Washington State University, Pullman, WA 99164–4234

Andrea Rahn
Department of Microbiology and Immunology, University of Western Ontario, London, Ontario N6A 5C1, Canada

Andrew Rasmussen
Department of Microbiology and Immunology, Emory School of Medicine, Rollins Research Center, 1510 Clifton Rd., Rm. 3152, Atlanta, GA 30322

Melanie Ratliff-Griffin
Department of Microbiology and Immunology, Emory School of Medicine, 3152 Rollins Research Center, Atlanta, GA 30322

Lise Rauscher
Laboratory of Plant Pathology, UMR 217 INRA/INA P-G, Université Paris 6, 16 rue Claude Bernard, F-75005 Paris, France

Kenneth N. Raymond
Department of Chemistry, University of California, Berkeley, CA 94720–1460

G. Marcela Rodriguez
TB Center, Public Health Research Institute, International Center for Public Health, 225 Warren Street, Newark, NJ 07103–3535

Michael P. Schmitt
Center for Biologics Evaluation and Research, Food and Drug Administration, 8800 Rockville Pike, Building 29, Room 108, HFM-437, Bethesda, MD 20892

Michael Tom Sebulsky
Department of Microbiology and Immunology, University of Western Ontario, London, Ontario N6A 5C1, Canada
Waltena Simpson  
Department of Biological Sciences, South Carolina State University,  
Orangeburg, SC 29117

Issar Smith  
TB Center, Public Health Research Institute, International Center for Public Health,  
225 Warren Street, Newark, NJ 07103–3535

P. Frederick Sparling  
Department of Medicine, University of North Carolina at Chapel Hill,  
Chapel Hill, NC 27599–7031

Igor Stojiljkovic  
Department of Microbiology and Immunology, Emory School of Medicine,  
Rollins Research Center, 1510 Clifton Rd., Rm. 3152, Atlanta, GA 30322

Michiel Stork  
Department of Molecular Microbiology L220, Oregon Health and Science University,  
3181 SW Sam Jackson Park Road, Portland, OR 97239

Terrence L. Stull  
Department of Microbiology/Immunology, University of Oklahoma Health Sciences Center,  
Oklahoma City, OK 73104

Dick van der Helm  
Department of Biochemistry and Microbiology, University of Victoria,  
P.O. Box 3055, Victoria, British Columbia V8W 3P6, Canada

Carin K. Vanderpool  
Department of Microbiology, University of Minnesota, MMC 196,  
420 Delaware Street S.E., Minneapolis, MN 55455–0312

Hans J. Vogel  
Structural Biology Research Group, Department of Biological Sciences,  
University of Calgary, Calgary, Alberta T2N 1N4, Canada

Christopher T. Walsh  
Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School,  
Boston, MA 02115

Cécile Wandersman  
Unité des Membranes Bactériennes, Institut Pasteur (CNRS URA 2172),  
25 rue du Dr. Roux, 75724 Paris Cedex 15, France

Angela Wilks  
Department of Pharmaceutical Sciences, School of Pharmacy,  
University of Maryland, Baltimore, MD 21201

Günther Winkelmann  
Institut für Mikrobiologie, Universität Tübingen, Auf der Morgenstelle 28,  
D–72076 Tübingen, Germany
Iron is one of the most abundant elements in the Earth’s crust. It also displays remarkable chemical properties; it has two stable valences and an extremely wide range of oxidation-reduction potentials. Given its abundance and properties, it is not surprising that most organisms evolved iron-dependent enzymes to perform many essential functions.

The importance of iron in microbial growth, metabolism, and interactions with the host has been recognized for many years. Studies such as those by Waring and Workman in the 1940s defined the iron requirements of several microorganisms. Subsequent studies showed that iron played a critical role in electron transport, metabolism, protection against oxidative stress, DNA metabolism, and regulation of gene expression.

Despite its abundance, iron acquisition represents a major challenge for many organisms. In the presence of oxygen, iron forms insoluble ferric hydroxides and the level of free iron in aerobic environments is below that required for microbial growth. For microbes that colonize or invade mammalian hosts, iron limitation is exacerbated by the presence of host high-affinity iron-binding proteins. Studies begun in the 1940s by Schade and Caroline demonstrated the presence of iron-binding proteins in host fluids and showed that these proteins inhibited microbial growth. Numerous studies over the ensuing 60 years have shown that competition for iron within the host is a critical factor in host-pathogen interactions.

Microbes have evolved an impressive array of systems designed to solubilize and capture iron from their environments. These include siderophores, low-molecular-weight iron-chelating compounds that are secreted into the environment, and cell surface receptors for host iron proteins. The growth-promoting effects of siderophores were detected as early as 1912, when Twort and Ingram reported a cell-associated growth factor in mycobacteria, but it was not until the 1950s that the isolation and structural characterizations of siderophores were first reported. Ferrichrome, a reddish-brown iron-binding
compound produced by the fungus *Ustilago*, was the first to be isolated and characterized. This work by J. B. Neilands was one of many pioneering studies from his laboratory that made enormous contributions to understanding not only the structure but also the biosynthesis, genetics, and regulation of expression of microbial siderophores. Neilands, along with Charles Lankford, put forward the hypothesis that these iron-binding compounds were involved in microbial iron transport and helped supply essential iron to the microorganism. Following the identification of ferrichrome, a large number of other siderophores have been described, and many details of their biosynthesis and transport have been elucidated. A number of these are described in this volume, although this description is by no means complete.

It was also recognized that iron could be extremely toxic to cells. Iron catalyzes the formation of potentially lethal reactive oxygen species. Therefore, the uptake of iron into cells must be tightly regulated, and negative regulation of genes by iron is a recurring theme in this book. This regulation extends beyond control of iron uptake to regulation of genes associated with virulence in a number of pathogens. Studies by Clarke of diphtheria toxin production and by van Heyningen of Shiga toxin synthesis showed that iron concentration was the environmental factor that determined the amount of toxin produced by the bacteria.

This book is an attempt to survey and consolidate the research on microbial iron transport that has taken place over the past 50 years. It is not intended to be an exhaustive catalog of everything that has been done. Rather, we hope to give the reader an overview of microbial iron transport and insight into where the field has been and where it is going. The authors were asked to provide a brief list of selected readings instead of a comprehensive bibliography of all the papers in their field. Any omission of important references should be blamed on the editors rather than on the authors of the chapters.

The availability of complete sequences of microbial genomes and increasingly sophisticated technology has led to an explosion of information in recent years, and many of the chapters focus on these recent advances. New iron transport systems have been identified based on analysis of genomes, and new models for transport have been suggested by crystallography and structural determinations of the membrane transport proteins. Some of these studies have raised as many questions as have been answered. One question that remains unresolved is the mechanism for transduction of energy from the inner membrane to the outer membrane receptors for transport of siderophores and other iron complexes through the outer membrane in gram-negative bacteria. It is well established that the cytoplasmic membrane protein TonB is required for this process, but precisely how it interacts with the receptors and how it transfers energy is still an open question. This question and possible models for TonB-mediated transport are described in several chapters of this book.

Overall, the book is organized into five sections. The first is an overview of the structures, chemical properties, and biosynthesis of the microbial products, siderophores and hemophores, used by these organisms to acquire iron. The second section describes the transport of these compounds into gram-negative bacteria and covers the structure of the receptors, their initial interaction with the ligand, the movement of the ligand through the outer membrane and the...
role of the TonB system in this process, and the structure and function of the
periplasmic binding proteins. A chapter on heme oxygenases, which remove
the iron from heme following transport, completes this section. The third
section gives a relatively complete picture of iron transport in the gram-negative
prototype, Escherichia coli K-12. Because this is the most extensively studied of
the gram-negative bacteria, there is a wealth of information on the genetics,
regulation, and structure of iron transport systems in E. coli K-12. The fourth
section is a collection of descriptions of iron transport systems in selected
pathogenic microorganisms. In many cases, the choice of organisms was
arbitrary. We have tried to include a representative selection of gram-negative,
gram-positive, and acid-fast bacteria and chose ones for which a relatively large
amount of information was available. However, many equally important
pathogens were omitted for the sake of brevity. Many of the iron transport
systems presented in this section are described relative to the prototype, and
the similarities to and differences from E. coli systems are noted. A chapter on
the potential exploitation of microbial iron transport systems for antibiotic
design completes this section. The book concludes with a section on iron
transport and ecology. This is an extremely important area but one that is often
overlooked in the emphasis on pathogens.

We are indebted to the many authors who gave generously of their time
in writing the chapters. It is our hope that this book will inform and stimulate
discussion of the importance of iron in biological systems.

JORGE H. CROSA
ALEXANDRA R. MEY
SHELLEY M. PAYNE
ABC proteins, 40–42
ABC transport systems, 78–80
ABC transporters, 113
Achromobactin, 403
structure of, 404
Actinobacillus, 72
Aerobactin, 6, 9–10, 203–205, 423–424
structure of, 204
synthesis of, 29, 203, 204
Albomycin, 122, 126–127, 162, 163, 416, 426, CP12
structure of, 158, 159
Alcaligin, 5, 8, 312–313, CP2
AlcS permease and, 316
Bordetella, biosynthesis genes, 314–316
siderophore system, genetic organization of, 314–315
system proteins and homologs, 315–316
ferric, transport mutants, AlcR-positive regulator and alc:ABCDER operon, 316
molecular structure of, 313–314
sensing, 318
siderophore utilization by, 313
Alcaligin receptor, FauA ferric, 316–317
Alcaligin system genes, transcriptional activation of, 317–318
transcriptional repression of, 317
Amoxicillin, 426
Ampicillin, 426, 428
Anguibactin
biosynthesis of, 243–244
regulation of, 245
transport of, 244–245
Anthrquinone carboxylic acid, conjugates of, 430
Antibiotics, siderophore, activity of, 423
bi- and tridentate, 424–426
catechol spermidine-based, 416, 426
for highly resistant targets, 426–430
monodentate, 423–424
multiwarhead, 430–431
natural, 416–417
redox-based drug release of, 431
synthetic, 425, 426–427
transport of, by FhuA, 163–164
Trojan horse, 126–128
with siderophore components, 425
Aryl carrier protein domain, 136–137
ATPases, heme-specific, 79
Azospirillum, 442
Azospirillum irakense, 442
Bacillibactin, 397–399
Bacillus, 396–400
Fur homolog regulation in, 399–400
iron transport in, 399
iron uptake in, genes involved in, 390
siderophores of, production in, 396–399
structures of, 396, 397
Bacillus anthracis, 396
Bacillus cereus, 396, 399
Bacillus megaterium, 396
Bacillus subtilis, 20–21, 178, 396, 397–398
Bacteria, gram-negative, iron uptake in, 178, 179
gram-positive, heme transport across outer membrane in, 80–81
iron assimilation in, 413–416
pathogenic, iron transport systems in, 197–433
siderophore biosynthesis in, 18–37

INDEXa

* a CP, color plate.
Bordetella, 311–328
  blu genes, regulation of, 324–325
  ferrimone-inducible iron acquisition in vivo by,
  325–327
  heme utilization by, 322–325
  heme utilization genes, 322–324
  regulatory genes of, 77
  xenosiderophore utilization by, 318–319
Bordetella avium, 83
Bordetella bronchiseptica, 311, 319, 325–327
Bordetella parapertussis, 311
Bordetella pertussis, 311, 319, 325–327
  in vivo growth of, 311–312
  iron acquisition by, 312–313
Bradyrhizobium, 469
Bradyrhizobium japonicum, iron uptake in, 477–478
Briicella abortus, 139
BtuB and TonB proteins, structures of, in absence and presence of vitamin B12, 153, CP15
N-domain of, 148–149, CP13
BtuB structure(s), 61–63, 155
β5-β6 loop in, 63
N-terminal plug domain and 22-strand β-barrel and, 62
BtuC protein, FhuB and, sequence homology between, 167, 168–169
Burkholderia, 451
Burkholderia cepacia, 83, 293–294
  siderophore-mediated iron uptake in, 307–308
Campylobacter jejuni, 106
Cancer, iron chelators for tumor inhibition in, 421
Carboxymycobactin(s), 361–362
  biosynthesis of, 362–363, 364
  capture of iron by, 364
  structure of, 362
Cefaclor, 426
Cephalexin, 426
Chorismate, 135
Chrysoactin, 403
  biosynthesis of, and degradation of, 405–407
  proteins involved in, 405, 406
  ferric, transport of, 404–405
  in plants, 409
  structural properties of, 403–404
  synthetase CbsF protein, structure of, 406, 407
Citrate, and iron uptake in P. aeruginosa, 295, 306
  ferric. See Ferric citrate uptake of, by rhizobia, 479
Citrate-hydroxamates, 447, 448
Citrate-mediated Fe3+ transport, 169–170
Cobalamin substrate, BtuB structures and, 61–63
Colibacillosis, 217
Colicin M, 162
Colicins, 103, 106–108
Coprogen, 122, 125, CP12
Corynebacterium diphtheriae, 77–78, 80–81, 87, 89, 90, 92, 186, 344–359, 368
  genetic map of ipr6 operon of, 347, 348
  heme iron regulation of hmuO and, 353–355
  heme-iron transport systems in, 348–350
  heme oxygenase in, 350
  heme utilization in gram-negative and gram-positive bacteria, compared, 352
hmuTUv heme transport locus in, 350–353
  iron transport systems in, 345–355
  siderophore-dependent transport in, 345–348
Corynebacterium glutamicum, 178, 397
Corynebacterium ureas, 80
Corynebactin, ferric, 7–8, CP1
Coxiella burnetii, 372
Cytochrome c maturation system and L. pneumophila iron acquisition, 382–383
Cytoplasmic membrane, transport of ferrichrome across, 164–168
Deinococcus radiodurans, 88–89
Desferal, 122, 125, 420, 439, 442, CP12
  conjugates of, 429, 430
  in iron overload syndrome, 417, 418
Desferrioxamine(s). See Desferal
Diethylenetriaminepentaacetic acid, 422
2,3-Dihydroxybenzoylserine, 134, 138
Diphtheria, characteristics of, 344–345
  forms of, 344
  Diphtheria toxin, 345
  iron regulation of, 355–359
  Diphtheria toxin repressor, 356
    functional domains of, 357, 358
    structural analysis of, 356–358
  Diphtheria toxin repressor-like repressors, family of, 358–359
Dipyridine, 422
2,6-Dithiocarboxylic acid, 420
DtxR, structure of, 189–190
Enterobacteriaceae, 104, 105, 181
  biosynthesis of, 24, 25, 134–138
  Bordetella, utilization genes, 319–321
    utilization system proteins and homologs, 320, 321
    circular dichroism spectrum of, 14, 15
    cluster genes, two-component regulatory systems of, 142
    ferric, 7–8, CP1
gene cluster, genes in, 135
  iron transport system, components of, 228–229
    structure of, 133, 134
  utilization genes, regulation of, 321–322
Enterochelin. See Enterobactin
Enwina, 402–412
  siderophore-mediated iron transport systems of, 403–407
Enwina carotovora, 402
Enwina chrysanthemi, 402, 403, 405, 407–411
  Fur-dependent iron regulation in, 407–410
  siderophore production by, 403
Enwina chrysanthemi 3937, regulation of pectinolysis and iron transport in, 409, 410
Enwina herbicola, 440
  animal-pathogenic, 216–217
  enterobactin locus in, 200
  extraintestinal isolates of, 215–216
  Fur protein of, 399–400
  Fur target sequences in, 193–194
  heme sources and, 278
  intestinal isolates of, 215
  K-12, iron transport, energetics, and regulation in, 131–196
  pathogenic, 199–218
ExbB proteins, 99
  TonB and ExbD proteins, 96–112
  topology of, 97
  transmembrane domains, conservation in, 108, 109
ExbD proteins, 99
  TonB and ExbB proteins, 96–112
  topology of, 97
  transmembrane domains, conservation in, 110
Exochelin(s), 361
  biosynthesis of, 29–30
Exomycobactins. See Carboxymycobactin(s)
Extragenic palindrome sequences, 144

Fe$^{3+}$ ion, 3–4
Fe$^{3+}$ transport, citrate-mediated, 169–170
Fe$^{2+}$ transport systems, 182–183
Fe-TRENCAM, 152
FecA, 51–52, 143–144, CP5–7
  apices and switch helices in, 55, 56–57, CP6–7
  crystal structures of, 155, 160, 161
  globular domain and lock region in, 58
  formation of transient channel in, 59–60, CP6, CP8
  N-domain of, 148–149, CP13
  N-terminal globular domain in, structure of, 53–54, CP5–7
  second site of interaction with TonB, 61, CP9
  signaling, and signaling pathway, 172–173
  structure of, reference points in, 58–59, CP8
  FecI σ factor, 173–174
FeEnt, adsorption and desorption of, 151
  binding of, conformational motion in L7 during, 151–152
  binding to FepA, 152
  interactions with TonB, 152–154
  loosely and tightly bound, 151
  transport through FepA, 152, CP14
FeEnt uptake, binding stage of, 149–152
  internalization stage of, 152–155, CP14
  site-directed mutagenesis in, 149–150
  two-site binding model of, 149–150
Feo genes, in bacteria, distribution of, 181–182
  regulation of expression of, 181
FeoB, and pathogenicity, 182
  G protein in, 178–180
  in L. pneumophila intracellular infection, 380–381
  transport of, by L. pneumophila, 379–381
FepA, 51, 52, CP5–7
  affinity for ligands, 151
  apices and switch helices in, 55, 56–57, CP7
  binding by, 140
  C-domain of, 149
  crystal structure of, 140, 155
  electron spin resonance spectroscopy of, 150
  FeEnt binding to, 152
  FeEnt transport through, 152, CP14
  fluorescence spectroscopy of, 150–151
  globular domain and lock region in, 58
  homology region identified with, 60–61
  lock region in, mutants of central residues of, 59
  N-domain of, 148–149, 156, CP13
  second site of interaction with TonB, 60–61
  selective permeability and, 155–156
  selectivity for ligands, 152
  transport biochemistry of, 147–157
FepB, 140, 143, 145
FepC, 144
FepD, 144
FepG, 144
Ferricactin, 455–456
Ferric citrate, and L. pneumophila, 378–379
  dinuclear, crystal structure of, 170
  induction by, 170–172
  transcription regulation, mechanism of, 174–175
  transport of, and signaling pathway, 172–173
  transport system, regulation by iron, 174
Ferric dicitrate, 208
Ferric iron binding protein, 117–118
Ferric reductases, L. pneumophila and, 383–384
Ferric uptake regulation gene. See Fur gene
Ferrichrome, 29–30, 126, 138–139, 152, 158, 163
Pseudomonas and, 441
  structure of, 158, 159
  transport of, 158–159
  across cytoplasmic membrane, 164–168
  across outer membrane, 160–164
  uptake of, interaction of components in, 168–169
Ferrichrome A, 8, CP4
Ferrichrome analogs, 423
Ferrienterobactin, uptake of, 139–141
Ferrienterobactin esterase, 138
INDEX

Ferrihemes, 83–84
Ferrioxamine B, 5, 8, CP3
and iron uptake in *P. aeruginosa*, 295, 306
Ferrioxamines, 438–439, 440
Ferrisiderophore receptor family(ies), 51, 53, CP5–7
Ferrous iron, transport of, 178–184, 208–209
by *L. pneumophila*, 379–381
uptake of, by rhizobia, 479–480
*sit* operon for, 209, 210
Ferrous iron genes, in *E. coli* K-12, 178–180
Ferrous iron transport system, 178–182, 234
FetA, as functional siderophore receptor, 269–270
Fhu iron transport system, components of, 228–229
FhuA, 51, 52, 60, 158–159, CP5–7
affinity for ligands, 151
and FhuD, interaction of, 168
apices and switch helices in, 55, 56–57, CP7
crystal structures of, 155, 160, 161
globular domain and lock region in, 58
*N*-domain of, 148–149, CP13
opening of channel in, 162
second site of interaction with TonB, 60–61
transport of antibiotics by, 163–164
wild-type, 162–163
FhuB and BtuC protein, sequence homology between, 167, 168–169
and FhuC, interaction of, 169
and FhuD, interaction of, 168–169
topology of, 165
FhuC and FhuB, interaction of, 169
FhuD, 140–141, 164–165
and FhuA, interaction of, 168
and FhuB, interaction of, 168–169
crystal structure of, 165
Fit ABC iron transport system, 233
Fiu ABC iron transport system, 233–234
5-Fluorouridine, 431, 432
FpvA, 299–300
in pyoverdine biosynthesis, 300–302
receptor-mediated gene expression of, 300
Freshwater environment, siderophores in, 440
Fungal siderophores, 6
Fur, 189–190
binding sequence, 190–192
functions of, 141–142
interaction with target sequences, consequences of, 192–193
regulation by, 142, 187
structure of, 189–190
target sequences, in *E. coli*, 193–194
target sites, 190–192
Fur boxes, and other regulatory elements, 194–195
Fur superfamily, in rhizobia, 482–484
as manganese-responsive regulator, 485
Ir* subgroup of, 483, 484–485
G protein, in FeoB, 180
Gingipains, of *P. gingivalis*, functions of, 337
of *Porphyromonas gingivalis*, role in heme acquisition, 335–339
structures of, 336
Gly residues, 60
Glycine, 60
Gonorrhea, 256
*Haemophilus*, 67, 273–292
heme and iron requirement and acquisition by, 273–276
hemoglobin of, 280–283
*Haemophilus ducreyi*, 83
heme sources and, 279
*Haemophilus influenzae*, 38–40, 43, 71, 72, 78, 273, 280–281
accessory proteins and, 289
genomic sequences of, 290
heme acquisition by, 284–285, 286, 287
heme and iron acquisition proteins of, 275–276
heme sources and, 278–279
hemoglobin/hemoglobin-haptoglobin binding proteins of, 281, 282
hemophore system of, 43
lactoferrin and, 288
regulation of iron and heme acquisition mechanisms by, 289–290
sources of iron for, 285–289
transferrin and, 288
utilization of hemoglobin-haptoglobin complexes by, 283–284
Haptoglobin, 67
Has hemophore system, 237–238
has operon, of *S. marcescens*, 44–45
*Helicobacter pylori*, 82–83, 181–182, 188
Heme, 206–208
acquisition mechanisms, regulation by *H. influenzae*, 289–290
acquisition of, by *H. influenzae*, 284–285, 286, 287
by *P. aeruginosa*, 308
by *P. gingivalis*, 331–332
gingipains of *P. gingivalis* in, 335–339
and iron acquisition proteins, of *H. influenzae*, 275–276
roles of, in vivo, 277
and iron requirement and acquisition, by *Haemophilus*, 273–276
as source of iron, pathogens using, 86
assimilation systems, 71
availability of, bacteria influencing, 76–77
bacteria binding or utilizing, 71
bacteria sensing presence of, 77–78
bacterial, and hemoprotein receptors, 66–85
uptake systems, 66, 68–70
binding and utilization, in *P. gingivalis*, 330–332
binding of, by *Legionella*, 383
cytoplasmic fate of, 81–82
degradation of, chemical steps in, 88
hemoglobin–bound, as iron source, 267–268
intercalation within DNA, 87
iron regulation of *hmuO* by, in *C. diphtheriae*, 353–355
membrane transport of, periplasmic and cytoplasmic, 78–80
methods of bacteria to acquire, 76–78
molecular weight of, 67
permeases and ATPases of, 79
regiospecificity of, 91–92
regulation of utilization of, in *P. gingivalis*, 339–341
sources of, 276–285
structure of, 67
transport of, in gram-negative bacteria, 71
in *P. gingivalis*, 339, 340
in virulence, 83–84
TollB proteins and, 82–83
transport systems, 67
of *Yersinia*, 234–238
unbound, 276–279
utilization of, by *Bordetella*, 322–325
in *C. diphtheriae*, 352
in rhizobia, 477
Heme acquisition pathways, 86–87
Heme acquisition systems, hemophore-dependent, 38–47
Heme–albumin complexes, 280
Heme assimilation systems, 74
Heme–binding proteins, in *P. gingivalis*, 333
Heme–hemopexin complexes, 279–280
Heme–iron transport systems, in *C. diphtheriae*, 348–350
Heme–mediated iron uptake systems, of *Vibrio*, 250–251
Heme oxygenase-like proteins, 90
Heme oxygenase proteins, amino acid sequence alignment of, 92, 93
Heme oxygenases, 87–89
bacterial, 86–95
bacterial phytochrome, 88–89
distribution among bacterial species, 92–93
in *C. diphtheriae*, 350
mammalian and bacterial, structural similarities in, 89–92
Heme periplasmic binding proteins, 79
Heme pocket, 90–91
Heme receptors, general, 72–76
Heme–specific ABC transporters, 78–80
Heme transport locus, *hmuTUV*, in *C. diphtheriae*, 350–353
Heme transport systems, phase-variable expression of, 78
regulated expression by bacteria, 77
*Y. enterolitica* and, 79–80
Heme transporters, and nonhomologous receptors, 76
Heme uptake systems, 80–81
Heme utilization genes, *Bordetella*, 322–324
Hemin. See Heme
Hemin utilization receptor, of *P. gingivalis*, 334–335
HemO, 88–89
Hemoglobin, 66, 67, 206–208
binding and utilization of, in *P. gingivalis*, 334
heme moieties in, 86
of *Haemophilus*, 280–283
receptors for, 267
Hemoglobin–haptoglobin complexes, utilization by *H. influenzae*, 283–284
Hemoglobin/haptoglobin binding proteins, of *Haemophilus influenzae*, 281, 282
Hemolysins, 67
of *Vibrio*, 252–254
Hemophore–dependent receptors, 72
Hemophore–receptor interactions, 43–44
heme delivery in, 44
Hemophore receptors, outer membrane, 43
Hemophores, 38–40, 87
α-helical C-terminal secretion signal of, 42
and siderophores, iron acquisition pathways of, 39
functions of, 46
HasA, 40, 41
heme acquisition systems of, 38–47
secretion of, 40–42
Hemoprotein–specific receptors, 72–76
HemR receptor, 333
Heterobactins, 445
High–molecular-weight protein 2, 35
HmbR, as receptor for hemoglobin, 267
Hmu/Hem hemoprotein transport and regulatory system, 235
Hmu/Hem uptake system, 234–237
Hmu transporters, identification of, 477
HmuR receptor, of *P. gingivalis*, 334–335
HpuA/HpuB receptor, 267–268
HpuAB, as receptor for hemoglobin, 267
function in humans, 268
genetics and regulation of, 268
α–Hydroxyacids, 208
*ibtA* and *fgfA*, in *Legionella* intracellular infection, 378
as *Legionella* siderophore, 379
IC202C, 420–422
IdeR, genes regulated by, 369
in *M. tuberculosis*, 368–369
Immunomodulators, 420–422
Intestinal tract, siderophore production in, 440–441
IraAb, 381–382
Iron, acquisition mechanisms, regulation by *H. influenzae*, 289–290
acquisition of, by *B. pertussis*, 312–313
Iron (continued)

by L. pneumophila, 384–385
cytochrome c maturation system and, 382–383
by P. gingivalis, 331–332
by streptococci, 394–396
in mycobacteria, 360–363
acquisition systems, in enteric pathogens, 200
and virulence of P. gingivalis, 341–342
assimilation of, in bacteria, 413–416
ferric, 18–19
octahedral configuration of, 18, 19
ferrimone-inducible acquisition of, by Bordetella, 325–327
ferrous. See Ferrous iron
free, for H. influenzae, 285–288
in hemoglobin, 86
in regulation of diphtheria toxin, 355–359
lactoferrin as source of, 263–267
regulation of, evolving complexity of, 188–189
Fur-dependent, in E. chrysanthemi, 407–410
 genetics of, 187–188
in mycobacteria, 368–370
required by P. gingivalis, 330
source(s) of, for H. influenzae, 285–289
for pathogens, heme and heme-bound proteins as, 86
hemoglobin-bound heme as, 267–268
steady-state distribution in humans, 87
storage of, by mycobacteria, 367–368
transport of, and ecology, 436–488
ferrichrome-and citrate-mediated, 158–177
in Bacillus, 399
in pathogenic bacteria, 197–433
nonsiderophore, in Staphylococcus, 392–394
siderophore-mediated, by P. aeruginosa, 294–304
in Legionella, 375–379
in Staphylococcus, 392–394
transport systems, enterobactin-dependent, of Yersinia, 227
FhuBCD siderophore-dependent, of Yersinia, 226–227
in biology of enteric pathogens, 209–217
nonsiderophore, 206–209, 211
of Legionella, 379–384
of Neisseria, 259–263
of P. gingivalis, 341–342
siderophore-dependent, of Yersinia, 221–229
siderophore-independent, of Yersinia, 230–234
siderophore-mediated, of Enterobacteriaceae, 403–407
uptake of, from transferrin, 262–265
in Bacillus, genes involved in, 390
in gram-negative bacteria, 178, 179
in P. aeruginosa, 305–306, 307
in rhizobia, 469–488
in Staphylococcus, genes involved in, 390–391
in Streptococcus, genes involved in, 390
pyoverdine-mediated, 463
siderophore-independent, by mycobacteria, 366–367
siderophore-mediated, by Neisseria, 268–270
by Vibrio, 242–250
in B. cepacia, 307–308
uptake systems, redundancy in Neisseria, 270–271
TonB-dependent, 270
Iron acquisition systems, of Neisseria, 258–259, 260
Iron heme transport protein, 333–334
Iron(III) chelators, therapeutic uses of, 413–433
Iron overload, siderophores in, 417
Iron-protoporphyrin IX. See Heme
Iron-responsive gene, regulation of, in rhizobia, 480–485
Iron transport systems, in C. diphtheriae, 345–348
irp6 operon, genetic map of, in C. diphtheriae, 347, 348
Irr, of Fur superfamily, 483, 484–485
Isopyoverdines, 455, 456
Johnne’s disease, 361
α-Ketoacids, 208
Klebsiella pneumoniae, 169
l-Lysine, 362
Lactoferrin, as iron source, 263–267
H. influenzae and, 288
interactions with L. pneumophila, 383
Lactoferrin LbpBA receptor, 263–265
Lactoferrin receptor, function of, in humans, 266–267
 genetics and regulation of, 265–266
Legiobactin, 376–377, 379
Legionella, 372–386
genetics and regulation of siderophore production by, 377–378
intracellular infection, 385
FeoB in, 381
ibTA and fgfA in, 378
nonsiderophore iron transport systems of, 379–384
siderophore-mediated iron transport in, 375–379
Legionella pneumophila, 372–373
FeoB and ferrous iron transport by, 379–381
ferric citrate and, 378–379
ferric reductases and, 383–384
hemin binding by, 383
importance of iron for, 374–375
interactions with transferrin and lactoferrin, 383
IraAB, functions of, 381–382
iron acquisition by, 384–385
cytochrome c maturation system and, 382–383
pvC-like genes in, 378
siderophore-mediated iron transport and, 375–379
virulence factors of, 373–374
Legionnaires’ disease, 372
pathogenesis of, 373
risk factors for, 373
Ligand competition studies, 10, 11–12
Ligand internalization, in FeEnt uptake, 154–155
Lipopolysaccharide O-antigen, 151
Lysine-N6-hydroxylation, 28
Malaria, 419
Malleobactin, 307
Maltose binding protein, 116–117
Manganese, 437
iron transport system of Y. pestis, 230–232
uptake of, sit operon for, 209, 210
Marine offshore environment, siderophores in, 440
Meningitis, bacterial, 256
Mesorhizobium, 469
Metal transporters, in outer membrane, 147–148
N-domains of, 156
structural features of, 148–149, CP13
Metallo-regulated genes, Fur-mediated repression of, 185, 186
5-Methylene furanone, generation of, 420
Micacocidin, chelation of ferric iron by, 30, 31
Microbacterium flavescens, 441
Microcin, 162
Mucormycosis, 448
Mycobacteria, as therapeutic agents, 417–419
biosynthesis of mycobactin and carboxymycobactin from, 363, 364
IdeR in, 368–369
Mycobacterium avium, 361
Mycobacterium bovis, 361
Mycobacterium fortuitum, 367
Mycobacterium intracellulare, 361
Mycobacterium leprae, 361
Mycobacterium neoaurum, 361
Mycobacterium paratuberculosis, 361, 366
Mycobacterium smegmatis, 28–29, 360, 361, 362, 365, 366, 367
Mycobacterium tuberculosis, 360, 361, 363, 365, 366, 367, 368, 417–419
biosynthesis of mycobactin and carboxymycobactin from, 363, 364
IdeR in, 368–369
Mycobacterium vaccae, 361
Mycobactin synthetic analogs, 418–419
Mycobactin(s), 361, 416–417
biosynthesis of, 362–363, 364
capture of iron by, 364–365
natural, 417–418
structure of, 362, 366
Myoglobin, 66
Myxochelins, biosynthesis of, 26
Nalidixic acid, conjugates of, 430
Neisseria, 256–272
adherence-related virulence factors of, 258
do not produce siderophores, 268–269
HpuAB of, 75–76
iron acquisition systems of, 258–259, 260
nonsiderophore iron transport systems of, 259–263
pathogenic, similar lifestyles of, 257
siderophore-mediated iron uptake by, 268–270
surface adhesins and, 257–258
virulence factors in, 256–257
Neisseria gonorrhoeae, 256
transferrin-iron acquisition system in, 263
Neisseria lactamica, 256
Neisseria meningitidis, 72, 78, 81, 82, 83, 88, 89, CP10, 256
HmuR of, 76
NGAL, 5
Nonribosomal peptide synthetases, 19–20, 21
NU216R, 381–382
Oregon Green maleimide, 101
Ornibactins, 306–307, 443
Ornithine, 28
Outer membrane, metal transporters in, 147–148
transport of ferrichrome across, 160–164
Outer membrane metal transport systems, 149
Outer membrane receptors, 148
Outer membrane transporters, non-hemophore-dependent, 71
Pantoeca agglomerans, 440
Pathogens, enteric, biology of, iron transport systems in, 209–217
gram-negative, and diseases caused by, 200
iron acquisition systems in, 200
Pectobacterium carotovorum, 402
Pectobacterium chrysanthemi, 402
Penicillin conjugates, 427
Peptides, nonribosomal, biosynthesis of, 19–20, 21
Periodontal diseases, 329
Periodontitis, 330
Periplasmic binding proteins, class 9, 118–119, 120
classification by clusters, 114
clustering of, 121
functions of, 113
in bacterial iron uptake, 113–129
structural features of, 114–116
topological arrangement of, 114–115
Plants, siderophores and, 440
Plasma, human, contents of, 66–67
Plasmodia, as therapeutic agents, 418–419
Plasmodium falciparum, 429
as therapeutic agents, 419
Plesiomonas shigelloides, 78
heme sources and, 279
Polycarboxylates, 447, 448
Porins, 51, 113
structure of, 155–156
Porphyromonas gingivalis, 72, 77, 78, 83, 329–343
acquisition of iron and heme by, 331–332
colonization by, 329
gingipains of, functions of, 337
role in heme acquisition, 335–339
structures of, 336
heme-binding proteins in, 333
heme transport in, 339, 340
heme utilization in, regulation of, 339–341
hemin binding and utilization in, 330–332
hemin utilization receptor and, 333
HemR receptor and, 333
HMUR of, 75
IhtB protein and, 333–334
iron requirements of, 330
iron transport systems of, and link to pathogenesis, 341–342
TonB-linked receptor and, 333
virulence of, influence of iron on, 341–342
Proteins, accessory, H. influenzae and, 289
as nonhomologous receptors, 76
heme periplasmic binding, 79
iron acquisition, and heme, roles of, in vivo, 277
iron transport, structural studies of, 49–129
outer membrane receptor, formation of transient channel in, 59–60
globular domains in, topology and structure of, 53–54
simultaneous sequence alignment of, 57–61
structure of, 51–65, CP5
bipartite gating, 52–53
two domains of, 51–52
periplasmic binding. See Periplasmic binding proteins
Proton motive force, 96–112
cytoplasmic membrane, protein shuttling and, 103–104
Protonophore carbonyl cyanide m-chlorophenyl hydratone, 103
Pseudobactin. See Pyoverdine(s)
Pseudomonas, 293–310
environmental fluorescent, diversity of, 451–468
ferrichrome and, 441
putative iron receptors and regulators in, 300, 301, 302
taxonomy of, 464–465
uptake post-outter membrane in, 306–307
Pseudomonas aeruginosa, 71, 72, 81, 82, 89, 105, 106, 293, 294
ferric pyoverdine receptor of, 299–300
Fur protein of, structure of, 189–190
heme acquisition by, 308
siderophore-mediated iron transport and, 294–304
siderophores of, 294–302
siderophores synthesized by, 428
Pseudomonas auvocacia, 462–463
Pseudomonas constanti, pyoverdine of, 453–454, 456, 462
Pseudomonas fluorescens, 72
Pseudomonas putida, 104–111, 319
Pseudomonas stutzeri, 439
Pseudomomin, 452
Pyochelin, 295, 302–304, 307, 452
biosynthesis of, and transport of, 302–303
genetics of, 303
regulation of production of, 303–304
Pyoverdine-quinoline antibiotic conjugates, 429
Pyoverdine(s), 428–429, 452
biosynthesis of, genetics of, 296, 297
biosynthetic pathway of, and structure diversity of, 459–460
chromophore level of, structure diversity at, 455–456
dicarboxylic side chain level of, structure diversity at, 454–455
environmental fluorescent, diversity of, 451–468
heterologous, uptake of, 302
iron uptake mediated by, 463
peptide level of, structure diversity at, 456–459
peptidic part of, amino acid composition of, 457, 458
physiological and biochemical features of, 453
regulation of production of, 297–299
side chains of, 454, 455
siderotyping of, 460–467
and environmental microbiology, 466–467
and phylogeny, 465–466
and taxonomy of, 464–465
benefits of, 466
IEF electrophoresis for, 460–461
pyoverdine-mediated iron uptake as method of, 461–463
siderotypes, and siderovars of, 463–464
structural features of, 453–460
structure of, 294–296
transport of, 299–300
Pyridine-2,6-bis(monothiocarboxylic acid), 452
Pyridoxal isonicotinoyl hydrazone, 422
Q fever, 372
Quinolobactin, 452
Ralstonia, 451
Rhizobactin, structure of, 472
Rhizobactin 1021, structure of, 472
Rhizobia, 77
ABC-type transporters of, 478–479
citrate uptake by, 479
Fbp-like proteins of, 478–479
ferrous iron uptake by, 479–480
free-living, iron uptake by, mechanisms of, 470–480
Fur superfamily in, 482–484
heme utilization in, 477
in silico analyses and "missing genes," 479–480
iron-responsive genes in, range of, 480
regulation of, 480–485
iron uptake in, mechanisms of, and regulation of, 469–488
regulators of, with broader regulatory spectrum, 481
Rpol of, 480–481
siderophore transporters of, 475–476
TonB and iron uptake in, 477–478
Rhizobium, 469
Rhizobium leguminosarum, 185, 471–473
iron uptake in, 477–478
RirA of, 481–482
siderophore synthesis and uptake in, 471–472
vicibactin biosynthetic gene cluster of, functions of, 474
Rhizobium loti-like bacterium, 442
Rhodobacterium sphaeroides, 92–93
Rhodococcus, 445
Rhodotorulic acid, 5, 8, 430, CP2
RhrA, regulator for RB1021 synthesis, 481
Rifamycin, 162
structure of, 158, 159
RirA, 481–482
Rpol, of R. leguminosarum, 480–481
Saccharomyces cerevisiae, 448–449
Salicylic acid, 452
Salmochehins, 202–203, 441
structure of, 202
Salmonella, 441
tenterobactin locus in, 200
environments harboring, 211
iron transport and pathogenesis in, 211–212
pathogenic, 199–218
Salmonella enterica, 169, 178, 211–213
heme sources and, 278
Salmycin, 416, 426
Schizokinen(s), 396–397
Serine, 362
Serratia marcescens, 40, 41, 72, 82, 104
has operon of, 44–45
hemophore of, crystal structure of, 42
receptor of, 43
TonB-like proteins in, 44
Shigella, 213–214
tenterobactin locus in, 200
pathogenic, 199–218
Shigella dysenteriae, 80, 81–82
heme transport locus of, 207
Shigella flexneri, 213–214
Siderophore antibiotics. See Antibiotics, siderophore
Siderophore binding proteins, 119–125
Siderophore-defective mutants, phenotypes of, 476–477
Siderophore-dependent iron acquisition pathways, 71
Siderophore-dependent transport, in C. diphteriae, 345–348
Siderophore-drug conjugates, antimicrobial studies of, 422–431
components of, 423
design of, 422–423
Siderophore-mediated iron transport systems, 199–206
Siderophore transport system, 415
Siderophores, α-hydroxy carboxylate-based, 414 and plants, 440
antibiotic properties of, 416–417, 424
as therapeutic agents, 416–417
bacterial and fungal, interrelationship between, 447–449
uptake in fungus, 448–449
bacterial catecholate, grouped according to structural elements, 446
binding of, 54–56, CP5–7
biochemical and physical properties of, 3–17
biosynthesis in bacteria, 18–37
carboxy late, 7
catechol-based, 414
catecholate, 6, 15, 16, 20–25
biosynthesis of, 22, 23
citrate-hydroxamate, 447, 448
classification of, 413
containing ligands binding iron(III), 413–415
degradation of, 441–442
denticity of, 12–14
description of, 242
ecological impact of, 442–447
ecology of, 437–450
electronic structure and spectra of, 14–15
five-member heterocyclic ring-containing, 30–35
fluorescent, 7
fungal, 6
grouped according to ecological habitat, 444–445
hydroxamate, 6–7, 25–30
biosynthesis in soil, 443, 446
scaffolds of, 28
structures of, 27
hydroxamate-based, 414
hydroxamate-type, binding sites in, 125–126, CP12
space-filling models of, 123
structures of, 122, 123
in aquatic environment, 440
internalization by, 154–155
mixed ligand, 414
of fluorescent Pseudomonas species, 452–453
Siderophores (continued)
  phenolate, 20–25
  biosynthesis of, 22, 23
  pM values of, 9–11, 13
  production of, in intestinal tract, 440–441
  in soil, 437–440
  protonation and iron formation constants of, 10, 11–12
  recognition of, 125–126
  secondary, 138–139
  solution thermodynamics of, 8–11
  stability of, conformational effects and, 14, CP2
  structure(s) of, 4–6, 7–8, CP1–4
  tetradentate, 5, 8, CP2
  types of, 4, CP1
  with common iron binding moieties, 413, 414

Sinorhizobium, 469
  Sinorhizobium meliloti, 28
  RB1021 siderophore of, synthesis and uptake of, 473–475, 476

Soft rot disease, 402–403

Soil, siderophore production in, 437–440

Staphylococcal siderophore transporter, 392

Staphylococci, 387–394
  iron-siderophore transport in, 390–392
  iron uptake in, genes involved in, 390–391
  nonsiderophore iron transport in, 392–394
  siderophores produced by, 387–390

Staphylococcus aureus, 67, 80, 387, 392–394
  Fur homologs of, 400
  genome, isd region of, 393
  heme transport system in, 81
  siderophore biosynthetic locus of, 388, 389

Staphylococcus epidermidis, 387, 392

Staphyloferrin A, 388

Staphyloferrin B, 388

Streptococci, 394–396
  iron acquisition by, 394–396
  iron uptake in, genes involved in, 390

Streptococcus intermedius, 394–396

Streptococcus pneumoniae, 394, 395, 396

Streptococcus pyogenes, 67, 80, 394, 395, 396
  heme transporters of, 76

Streptomyces pilosus, 438–439

Streptomyces, 437–440

Synchocystis, 367

TbpA, 259–260

TbpB, 259–260

Threonine, 362

TonA mutant phenotypes, 96–97

TonB, in rhizobia, 477–478

TonB-like proteins, 44, 56
  sites of FecA interaction with, 61, CP9
  sites of FhuA interaction with, 60

TonB–linked receptor, P. gingivalis and, 333

TonB mutant phenotypes, 96–97

TonB proteins, 97–98
  and BtuB, structures of, in absence and presence of vitamin B12, 153, CP15
  and ExbB and ExbD proteins, 96–112

Transferrin, as iron source of Neisseria, 259–263
  H. influenzae and, 288
  interactions with L. pneumophila, 383
  iron uptake from, 262–263

Transferin-binding proteins, 259–260

Transferin–iron acquisition system, in N. gonorrhoeae, 263

Transferin–iron internalization, proteins in, 260–261

Transmembrane signaling device, induction of ferric citrate transport system by, 170–175

Treponema pallidum, 118

Trihydroxamate, isocyanurate-based, drug conjugates of, 431, 432

Tuberculosis, 417–419

Ustilago sphaerogena, 158

Vibrio, 241–255
  energy-transducing complexes of, 252, 253
  siderophore-mediated iron uptake by, 242–250
  siderophores of, structures of, 243
  transporters in, 251–252


Vibrio vulnificus, 76, 77, 241, 242, 247–248, 252

Vibriobactin, biosynthesis of, 32–35, 245–247
  location of, 245
  regulation of, 247
  transport of, 247

Vibrio ferruginosus, 249–250

Vicibactin, structure of, 472
  synthesis of, and transport of, 471–473
  pathway of, 474

Virulence, bacterial, heme transport in, 83–84
Vitamin B$_{12}$, structures of TonB and BtuB in absence and presence of, 153, CP15
Vitamin B$_{12}$ transporter, structure of, 165–167
Vulnibactin, 248

*Xanthomonas campestris*, 106
Xenosiderophore, utilization by *Bordetella*, 318–319
Xenosiderophore transport systems, 205–206, 304
*Xylella fastidiosa*, 106

*Yersinia*, 219–240
   HemR and HmuR of, 73–75
   iron regulation and storage by, 238
   pathogenesis of, iron and hemoprotein transport systems and, 224
*Yersinia enterocolitica*, 72, 73, 74, 81, 86–87, 219, 223, 226–227, 236, 237, 238
   heme-specific ABC transport by, 79–80, 234–235
*Yersinia pestis*, 32, 72, 78, 219–222, 226–227, 236–237, 238, 407
derivatives of, gene fusion in, 225
manganese ABC iron transport system of, 230–232
Yfe iron transport system of, 230–232
Ysu and Ynp siderophore biosynthesis systems, 227–229
*Yersinia pseudotuberculosis*, 219, 223, 226–227
Yersiniabactin, 32–35, 205
   iron transport system, 221–226
   model of, 222
   structure of, 221, 366
Yfu iron transport system, 232–233
Yiu iron transport system, 232–233
Ynp iron transport system, components of, 228–229
Zur protein, 186–187