

Preface

It is astonishing to realise that a slim volume of some 260 pages (Crichton, 1991), first conceived in the course of a discussion with the egregious Ellis Horwood at the Christmas buffet of the Royal Society of Chemistry Inorganic Biochemistry Discussion Group, has grown to such a size. Ellis Horwood had established his own scientific publishing house, Ellis Horwood Limited, based in the charming old Market Cross House in the West Sussex town of Chichester and, with his usual inimitable enthusiasm, he persuaded me – rather easily as it turned out – to contribute to his series of *Inorganic Chemistry* books. The outcome was *Inorganic Biochemistry of Iron Metabolism*, and any thoughts of subsequent editions had certainly not crossed my mind.

I say rather easily, because since the publication of the proceedings of the second meeting on proteins of iron storage and transport (Crichton, 1975), there had been a void which was crying out to be filled for a definitive work which would bring together an overview of the dramatic developments which had been taking place in the field of iron metabolism since then. All of the manuscripts of the presentations at that meeting in Louvain-la-Neuve were incorporated into the book *Proteins of Iron Storage and Transport in Biochemistry and Medicine*, produced by North Holland/American Elsevier in record time – the meeting was held from 2nd–5th April, 1975 and the book (all 454 pages) appeared in July of that year! They included the contribution by Jean Montreuil and Genevieve Spik from Lille, who arrived without a manuscript, but after being closeted in an office with an English-speaking secretary, duly produced the goods before the end of the meeting, as well as Clem Finch's Concluding Remarks recorded on a Dictaphone at the end of the meeting, typed that evening during the concluding Banquet, and duly dispatched, corrected, the following morning along with all of the other camera-ready texts. This volume, which represented the first time that all of the major figures on the iron scene had published jointly what was a sort of 'state of the art of iron metabolism, 1975', sold over 600 copies, and was still being cited more than a decade after the meeting itself. However, despite intermittent efforts after the New York meeting in 1977, the Sapporo meeting in 1983 and the Lille meeting in 1985 (Brown *et al.*, 1977; Uroshizaki *et al.*, 1983; Spik *et al.*, 1985), there was a real potential for a book that would bring together all aspects of iron metabolism.

My decision to undertake this ambitious project was greatly facilitated by the fact that I was in line for a sabbatical – in reality six rather than 12 months – which I spent at the invitation of Professor Robert Freedman in the Biology Department of the University of Kent in Canterbury. Ironically (no pun intended) for the author of a book on inorganic chemistry, my office was in the Chemistry Department. In those prehistoric times one hunted down references on the shelves of the University library overlooking the majestic and historical Cathedral, photocopied them (a new innovation), and then read them, highlighting the important sections. When the references (hunted down in *Chemical Abstracts*) were not available in Canterbury, one undertook a day trip to London to consult the Science Library there. Then, with reams of fluorescent highlighted papers, one sat down to write one's own text, mostly in my flat on the Canterbury Road in the agreeable seaside town of Whitstable, with its beach and bracing sea air.

The outcome, in 12 chapters, is quite similar to this 4th edition, dealing with iron chemistry, the importance of iron in biology, microbial, plant and fungal iron uptake, transferrin and its receptor (a relatively recent discovery), intracellular iron, iron homeostasis, iron absorption, iron deficiency and overload, iron and oxidative damage and finally, iron and infection. There were some 800 references in all, regrouped at the end of the book, in the classical chemical presentation without title, but with the final page number. I would think that, with the resources then available, I had read the abstracts of all of the articles (in *Chemical Abstracts*) and read the better part of 50–60% of the most important articles. The figures were entirely in black and white!

When, ten years later, I undertook a 2nd edition (Crichton, 2001), the title – now *Inorganic Biochemistry of Iron Metabolism. From Molecular Mechanisms to Clinical Consequences* – had been transferred to John Wiley & Sons, and the 326-page outcome even had a central glossy page insert which included 16 ‘Plates’ of coloured figures (all of the others were black and white). For this edition I enlisted the help of six colleagues, Volkmar Braun and Klaus Hantke for microbial iron uptake, Jo Marx and Manuela Santos for the pathophysiology of iron deficiency and iron overload, Roberta Ward for the chapter on oxidative stress, and Johann Boelaert for iron and infection. There were some 1500 references, this time regrouped at the end of each chapter, but again without titles. Once again, it is probable (I cannot speak for my colleagues) that at least the abstracts of the papers cited had been read as well as most of the key articles.

By the time of the 3rd edition (Crichton, 2009), I had returned to the essentially single author format, with two chapters being entrusted to my long-term collaborator, Roberta Ward. Reflecting the way the field was growing, the microbial iron chapter included a view of intracellular iron metabolism, while the plant and fungal chapter highlighted the extraordinary developments in our understanding of yeast iron uptake systems. Although discovered just after the 2nd edition, hepcidin was relegated to the iron absorption chapter in which systemic iron balance was reviewed. The chapter on iron and infection was replaced by a new chapter on brain iron homeostasis and its perturbation in neurodegenerative diseases. Virtually all of the figures were in colour, and the 2200 references this time included titles (which makes for a lot more work – as a colleague remarked, “you can always invent the final page number, but the title.....?”, yet I think it is more useful in deciding if the reader really wants to hunt it down).

This 4th edition has reached even larger dimensions, with the number of references soaring to over 3500. As in the previous edition, we begin with a chapter on the solution chemistry of iron in biological media, the biologically very important interactions of iron with dioxygen, followed by a short review of hydrolysis of iron salts, the characterisation of ferrihydrite and its ageing to more crystalline products. The chapter concludes with a section on biomineralisation, with particular emphasis on magnetite formation by magnetotactic bacteria. The essential role of iron in biology is once again reviewed in Chapter 2, illustrated by examples drawn where possible from the recent literature.

The section on microbial iron has been subdivided this time into two chapters to take account of the important role of iron acquisition in the virulence of microbial pathogens and, in particular, as potential antimicrobial therapeutic targets. Chapter 3 discusses iron uptake from ferric siderophores in Gram-negative and Gram-positive bacteria, as well as the systems used by both classes of bacteria to take up Fe^{2+} . Iron release from siderophores and intracellular iron metabolism are then reviewed, and the chapter concludes with a discussion of the mechanisms involved in the regulation of gene expression by iron.

Iron sequestration provides the innate host defence, known as nutritional immunity, which leads bacterial and fungal pathogens to scavenge iron from their hosts. Chapter 4 is devoted to iron assimilation by pathogens, beginning with an overview of host defence mechanisms and

nutritional immunity. The importance of pathogenicity islands, horizontally transferred mobile genetic elements involved in the dissemination of antibiotic resistance and virulence genes in pathogenic organisms, which frequently also encode iron uptake systems, specific to pathogenic strains (Gyles and Boerlin, 2014) is then outlined. Pathogen-specific iron uptake systems, involving pathogen-specific siderophores, host sources of iron such as transferrin, lactoferrin and haem, ferrous iron and ferric citrate, are then analysed. The structural basis of iron piracy by pathogenic *Neisseria* from human transferrin has been elucidated (Noinaj *et al.*, 2012). These studies establish a rational basis for the host specificity of TbpA, the TonB-dependent outer membrane transporter for human transferrin, show how TbpA promotes iron release from transferrin, and elucidate how TbpB, the lipoprotein coreceptor, facilitates this process. Recent cloning and sequencing of transferrin orthologues from 21 hominoid monkey species (Barber and Elde, 2014) revealed that hominoid transferrin has undergone recurrent positive selection at the binding interface with bacterial TbpA, providing a mechanism to counteract bacterial iron piracy. The regulation of pathogen iron uptake by Fur and Fur homologues, and by pathogen ECF sigma factors, are discussed, and we conclude with a brief outline of the strategies employed by opportunistic fungal pathogens, which represent a growing health threat, to acquire iron from their host.

Our understanding of iron uptake by plants and fungi has been greatly influenced by the fulgurant progress in genome sequencing, and Chapter 5 presents our current views on this area, with its important consequences for agriculture. Iron is the most commonly deficient micronutrient in the human diet, with iron deficiency affecting around 1.6 billion people (Chapter 11), and plants represent one of the principal sources of our dietary iron. However, while iron plays a key role among minerals in improving plant product quality, and is an important determinant in photosynthetic efficiency in algae and higher plants (Briat *et al.*, 2015), Fe deficiency – notably in calcareous soils – is very common. As our understanding of iron assimilation and distribution pathways in plants evolves, this information will assist in the development of strategies to improve both iron content and bioavailability of the edible parts of crops, in order to better improve our diet. Chapter 5 begins with a review of iron uptake by plant root systems, together with long distance iron transport in graminaceous and non-graminaceous plants, followed by a review of new tools in plant research, including integrative-omic analyses, and a discussion of intracellular plant iron metabolism and homeostasis. The final part of the chapter gives an account of iron uptake, metabolism and regulation in fungi.

Chapter 6 deals with mammalian cellular iron uptake and export, as in previous editions, beginning with the transferrin superfamily. Most transferrin family members have a familiar bilobal structure, resulting from an ancient gene duplication, with an iron-binding site in each of two homologous lobes. However, in the course of evolution transferrin homologues with a variety of domain architectures are found, including monolobals, bilobals with one or both iron-binding sites abrogated, bilobals with long insertions or with membrane anchors, and even trilobals (Gaffney and Valentine, 2012). Indeed, quite a number of the members do not appear to play any role in iron binding or transport. A discussion of the detailed structure of transferrins is then followed by an analysis of the binding not only of iron, but also of other metal ions, to the transferrin molecule. The structure of the transferrin receptor and its central role in cellular iron uptake from transferrin precedes a summary of other potential sources of cellular iron uptake, and the chapter concludes with an account of ferroportin and its role in iron export.

In Chapter 7 an overview of mammalian iron metabolism is presented, including an account of the diverse ways in which different cells of the body handle iron. The erythrocyte-forming cells of the bone marrow are the main iron *importers*, consuming most of the plasma iron for haem synthesis and its incorporation into the oxygen transport protein haemoglobin. In contrast, both the

enterocytes of the gastrointestinal tract and the macrophages of the spleen and liver (Kupffer cells) are involved in the *import* and *export* of iron. The former capture dietary iron and then export it to the rest of the body. In contrast, splenic macrophages acquire iron from the phagocytosis of effete red blood cells, and then export it through transferrin for the requirements of other cells of the body, with the bulk going to the erythroid bone marrow. Dietary iron absorption from the intestinal mucosa in mammals concludes the Chapter, with an assessment of dietary sources of iron, and a review of the mechanisms of mucosal iron absorption.

Chapter 8 regroups a detailed analysis of our present understanding of intracellular iron utilisation in mammals, opening with a description of intracellular iron pools. Most of the iron taken up by the cell enters the kinetically labile iron pool (LIP) in the cytosol, the functional attributes of which were first presciently described by Allan Jacobs in 1977 (Jacobs, 1977), although its precise nature still seems to be uncertain (Cabantchik, 2014). While most of the iron in the LIP is destined for the mitochondria, there are increasing indications that members of the poly C binding protein (PCBP) family have iron chaperone activity, supplying iron both to ferritin and to enzymes of the family of iron and α -ketoglutarate-dependent dioxygenases (Shi *et al.*, 2008; Nandal *et al.*, 2011). Mitochondrial iron uptake and storage are briefly discussed before a detailed account of the current views on Fe-S cluster biosynthesis, Fe-S protein biogenesis and the maturation of cytosolic and nuclear Fe-S proteins (Stehling *et al.*, 2014). The chapter concludes with a discussion of haem biosynthesis and catabolism, the latter focusing on haem oxygenase and its activation.

Chapter 9 is devoted to iron storage proteins, beginning with a presentation of the ferritin superfamily, made up of at least 12 ‘subfamilies’ (see Figure 9.1), of which the ferritins are the most abundant. Within the superfamily there are three distinct types of iron storing and detoxifying proteins which constitute the ferritin subfamily: the classical 24-meric ferritins; the haem-containing 24-meric bacterioferritins of prokaryotes; and the prokaryotic 12-meric Dps proteins, which bind to and protect DNA. All three are derived from far more simplistic rubrerythrin-like molecules, which play roles in defence against toxic oxygen species (Andrews, 2010). The extensive structural studies on the ferritins, Dps proteins and rubrerythrins are then reviewed, and this first section concludes with an account of the mineral core and the lysosomal degradation product of ferritin, haemosiderin. The second part of the chapter includes a detailed discussion of mechanisms involved in the uptake and release of iron by ferritins and Dps proteins. While there is considerable agreement on how iron enters the protein shell, and on the role of the ferroxidase centre in iron oxidation, there is still some controversy concerning the mechanism of iron storage by ferritins (Honarmand Ebrahimi *et al.*, 2014; Bradley *et al.*, 2014), although the opposing views may end up being reconciled. The chapter concludes with a brief overview of recent biotechnological applications of ferritins.

The exciting recent developments in our understanding of cellular and systemic iron homeostasis and their regulation are outlined in Chapter 10. The role of the IRE/IRP system in the regulation of cellular iron metabolism has undergone much refinement in detail, but the overarching picture of elegance in regulating mRNA translation remains. That is, when iron is scarce the uptake pathways are turned on and the storage and utilisation pathways are turned off, with the reverse happening in iron abundance (Kühn, 2014). Since the serendipitous discovery of its involvement in iron metabolism (Nicolas *et al.*, 2001; Pigeon *et al.*, 2001), the key role of hepcidin in regulating systemic iron homeostasis has become the brightest beacon on the iron scene. As Tom Ganz has elegantly put it, “The iron hormone hepcidin and its receptor and cellular iron exporter ferroportin control the major fluxes of iron into blood plasma: intestinal iron absorption, the delivery of recycled iron from macrophages, and the release of stored iron from hepatocytes” (Ganz, 2013). Finally, over the last few years the role of hypoxia-inducible factors (HIFs), notably HIF-2, in iron homeostasis has emerged. These transcription factors regulate responses to hypoxia but also regulate key proteins of iron

metabolism (Simpson and McKie, 2015). The way in which the activity of hepcidin, the master regulator of systemic iron homeostasis, the cellular IRE/IRP system, and HIF-2 are coordinated will no doubt gradually begin to be better understood. The interplay between the three regulatory systems – the IRE/IRP system, the HIF system and the ultimate key orchestrator of systemic iron homeostasis, the hepcidin/ferroportin system – is slowly beginning to be understood.

Important questions concerning the integration of these regulatory systems remain, some of which are addressed in Chapter 11, which reviews our current understanding of human iron deficiency and iron overload (both hereditary and acquired), together with an assessment of their therapy. The mainstay of iron-deficiency anaemia (IDA) treatment and prevention remains iron fortification of staple foodstuffs, which is considered to be the most cost-effective method for providing additional iron for populations with a high prevalence of IDA (Lynch, 2011). This in turn underlines the importance of developing agronomic, plant breeding and transgenic approaches to increase the Fe content and the bioavailability of the edible parts of crops in order to improve the human diet (Briat *et al.*, 2015). Introduction of the orally active chelator deferasirox (DFX, Exjade®; Novartis Pharma AG, Basel, Switzerland) has allowed a greater diversity of therapeutic strategies for the treatment of acquired iron overload (Saliba *et al.*, 2015). However, as has been pointed out by Ioav Cabantchik (Cabantchik *et al.*, 2013), these chelation regimens might not be suitable for treating disorders of iron maldistribution, as those are characterised by toxic islands of siderosis appearing in a background of normal or subnormal iron levels (e.g. sideroblastic anaemias, neurosiderosis and cardiosiderosis in Friedreich's ataxia and neurosiderosis in Parkinson's disease). New therapeutic approaches involving the normalisation of hepcidin levels in order to lower serum iron levels are being pursued in animal models of haemochromatosis and of acquired iron overload (Ganz, 2013; Schmidt and Fleming, 2014), with particularly promising results in animal models, notably of additive effects when combined with chelation therapy (Schmidt *et al.*, 2015).

Chapter 12 is a new addition, penned by my long-suffering collaborator of many years, Professor Roberta Ward, on the relationship between iron and the body's defence against inflammation and infection, the immune system. Iron and immunity are closely linked. Iron withholding by many of the proteins involved in iron metabolism is a major strategy in preventing bacteria from utilising iron for growth. The monocytes, macrophages, microglia and lymphocytes of the innate immune system are able to combat bacterial insults by carefully controlling their iron fluxes, while a variety of effector molecules, including hypoxia factor-1 and haem oxygenase orchestrate the inflammatory response by mobilising cytokines, neurotrophic factors, chemokines and reactive oxygen species (ROS) and reactive nitrogen species (RNS). Both iron excess or deficiency can adversely affect the ability of these cells to respond to the bacterial insult.

Chapter 13, as in previous editions, examines the dark side of iron's interactions with molecular oxygen. After a brief introduction, the physiological context in which the different ROS and RNS are formed are reviewed, as are the cellular defence mechanisms against ROS and RNS. Particular emphasis is placed on the thioredoxin/peroxiredoxin system (Lu and Holmgren, 2014). We are all familiar with signalling pathways, which involve conformational changes induced by altering the charge of proteins, either by phosphorylation/dephosphorylation via kinases/phosphatases, or by Ca^{2+} -binding. However, we have become increasingly aware during the past few decades that, whereas high levels of ROS and RNS have deleterious effects, at low concentrations they can play an important signalling role in the control of cellular function by responding to changes in the intracellular redox potential. The chapter ends with an overview of the role of ROS and RNS in causing oxidative damage, by catalysing pathways which result in essentially irreversible modifications of amino acid residues in proteins.

Since the 2nd edition, a chapter has been devoted to the interactions between iron and other metals, and the 4th edition is no exception. Both experimental data and clinical findings have indicated that diseases of iron metabolism can be associated with alterations in the metabolism of other essential metal ions, particularly divalent cations (Loréal *et al.*, 2014). Chapter 14 first deals with the interactions of iron with the essential metal ions copper, zinc, cobalt, manganese and, for the first time, despite its quite different coordination chemistry, calcium. Exactly how Ca^{2+} interferes with iron transport is not clear, although voltage dependence or intracellular Ca^{2+} signalling seems to be ruled out (Shawki and MacKenzie, 2010). There are many toxic 'heavy' metals, some of which have gained access to the human population as a result of our own activities, such as the leaching of aluminium, the most abundant metal in the Earth's crust, into our environment as a consequence of the acid rain generated by emissions of sulphur dioxide and nitrogen oxide; in some regions of Eastern Europe the soil pH values fell below 3. We discuss the interference of the nonessential, toxic metals lead, cadmium and aluminium with iron.

The final chapter, also written in collaboration with Roberta Ward, addresses a subject which has been of particular interest to both of us over the past decade (Crichton and Ward, 2006, 2014; Ward *et al.*, 2013), namely the role of iron in neurodegenerative diseases. When we first advanced the idea that many neurodegenerative diseases involved dysfunction of brain homeostasis of essential metal ions – notably iron, copper and zinc (Crichton and Ward, 2006) – the evidence was not nearly as convincing as it is today. Sadly, our understanding of brain iron homeostasis is still in its infancy, but neurodegeneration with brain iron accumulation now covers – as the reader can see in Chapter 15 – a wide range of neurodegenerative diseases, including Parkinson's, Alzheimer's and Huntington's diseases and multiple sclerosis.

So, there have been many developments in iron metabolism since the last edition, and I assume the entire responsibility for any omissions or errors that have undoubtedly crept into my text, if only on account of the length and breadth of its subject matter. I would also like to thank Roberta Ward for her important contributions to Chapters 12 and 15, and to the many colleagues, who have given me useful advice.

Robert Crichton
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