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REVIEW ARTICLE

Towards a unifying, systems biology understanding of large-scale cellular death and destruction caused by poorly liganded iron: Parkinson's, Huntington's, Alzheimer's, prions, bactericides, chemical toxicology and others as examples

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Abstract Exposure to a variety of toxins and/or infectious agents leads to disease, degeneration and death, often characterised by circumstances in which cells or tissues do not merely die and cease to function but may be more or less entirely obliterated. It is then legitimate to ask the question as to whether, despite the many kinds of agent involved, there may be at least some **unifying mechanisms** of such cell death and destruction. I summarise the evidence that in a great many cases, one underlying mechanism, providing major stresses of this type, entails *continuing and autocatalytic production* (based on positive feedback mechanisms) of hydroxyl radicals via Fenton chemistry involving **poorly liganded iron**, leading to cell death via apoptosis (probably including via pathways induced by changes in the NF-κB system). While every pathway is in some sense connected to every other one, I highlight the literature evidence suggesting that the degenerative effects of **many diseases and toxicological insults converge on iron dysregulation**. This highlights specifically the role of iron metabolism, and the detailed speciation of iron, in chemical and other toxicology, and has significant implications for the use of iron chelating substances (probably in *partnership* with appropriate antioxidants) as nutritional or therapeutic agents in inhibiting both the progression of these mainly degenerative diseases and the sequelae of both chronic and acute toxin exposure. The complexity of biochemical networks, especially those involving autocatalytic behaviour and positive feedbacks, means that multiple interventions (e.g. of iron chelators plus antioxidants) are likely to prove most effective. A variety of systems biology approaches, that I summarise, can predict both the mechanisms involved in these cell death pathways and the optimal sites of action for nutritional or pharmacological interventions.

Keywords Antioxidants · Apoptosis · Atherosclerosis · Cell death · Chelation · Chemical toxicology · Iron · Neurodegeneration · Phlebotomy · Polyphenols · Sepsis · SIRS · Stroke · Systems biology · Toxicity

Abbreviations

Aβ	β-amyloid
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis (Lou Gehrig's disease)
BSE	Bovine spongiform encephalopathy
CJD	Creutzfeldt-Jakob disease
CNS	Central nervous system
EAE	Experimental autoimmune encephalomyelitis
GBA	Glucocerebrosidase
HD	Huntington's disease
Htt	Huntingtin protein
MCMC	Markov chain Monte Carlo
MIRIAM	Minimum information requested in the annotation of biochemical models
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS	Multiple sclerosis
PD	Parkinson's disease
RNS(s)	Reactive nitrogen species
ROS(s)	Reactive oxygen species
SBML	Systems biology markup language

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SBRML	Systems biology results markup language
SIRS	Systemic inflammatory response syndrome
TCDD, ‘dioxin’	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TSEs	Transmissible spongiform encephalopathies
2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid

Introduction

As a transition metal that can exist in several valencies, and that can bind up to six ligands, iron is an important component of industrial catalysts in the chemical industry (Hagen 2006), especially for redox reactions. Its catalysis of specific reactions requires rather exact architectures at the catalytic centre, and indeed much of the art and science of catalyst production involves determining and synthesising them. Nearly half of all enzymes are metalloproteins (Waldron et al. 2009), and iron is also of considerable importance in biology as a component of all kinds of metalloproteins (Andreini et al. 2008, 2009) from haemoglobin to cytochromes, as well as in the directed evolution of *novel* enzyme activities (Pordea and Ward 2008; Que and Tolman 2008; Turner 2009). When serving in enzymes, the iron is normally safely liganded, and any reactions catalysed are usually fairly specific. However, as is widely recognised, iron can also have a dark side (Kell 2009a), in that when it is not properly liganded (Graf et al. 1984), and in the ferrous form, it can react with hydrogen peroxide (produced by mitochondria (e.g. Brennan and Kantorow 2009; Fato et al. 2008; Orrenius et al. 2007) or (per)oxidases (Bedard and Krause 2007; Cave et al. 2006) via the Fenton reaction (Goldstein et al. 1993; Kruszewski 2003; Toyokuni 2002; Wardman and Candeias 1996; Winterbourn 1995), leading to the very reactive and damaging hydroxyl radical ($OH^{\bullet}$)

$$Fe(II) + H_2O_2 \rightarrow Fe(III) + OH^{-} + OH^{\bullet} \qquad (1)$$

Superoxide (also produced by mitochondria) can react with ferric iron in the Haber-Weiss reaction (Kehrer 2000) to produce Fe(II) again, thereby effecting redox cycling of the iron (Fig. 1):

$$O_2^{\bullet -} + Fe(III) \rightarrow O_2 + Fe(II) \qquad (2)$$

Ascorbate (vitamin C) can also replace $O_2^{\bullet -}$ for reducing the Fe(III) to Fe(II) (Hershko and Weatherall 1988), as can other reducing agents, and indeed too low a redox poise leads to DNA damage (e.g. Li and Marbán 2010; Seifried et al. 2007).

The hydroxyl radical is exceptionally reactive and damaging to cellular components, and, for instance, can liberate further Fe(II) from iron-sulphur centres and other iron-containing compounds such as ferritin (Arosio et al. 2009), thereby driving reaction (1) in an autocatalytic, runaway kind of reaction. This kind of phenomenon has the potential to overwhelm any kinds of attempts at repair, and inflammation and oxidative stress are the hallmarks of each of the conditions I summarise. Related reactions include peroxynitrite production (from the reaction of NO and superoxide) (Babior 2000; Beckman et al. 1990; Beckman and Koppenol 1996; Goldstein and Merényi 2008; Koppenol et al. 1992; Murphy et al. 1998; Pacher et al. 2007; Pavlovic and Santaniello 2007; Pryor and Squadrito 1995; Radi et al. 2001, 2002; Rubbo and O’Donnell 2005; Rubbo et al. 2009; Smith et al. 1997b; Squadrito and Pryor 1998; Szabo 1996; Szabó et al. 2007; Torreilles et al. 1999; White et al. 1994; Zimmet and Hare 2006). These can lead to nitrotyrosine (Beckman 1996; Goldstein and Merényi 2008; Herce-Pagliai et al. 1998) (a reaction catalysed by poorly liganded iron, Beckman et al. 1992), or nitro-fatty acid (Aslan et al. 2001;

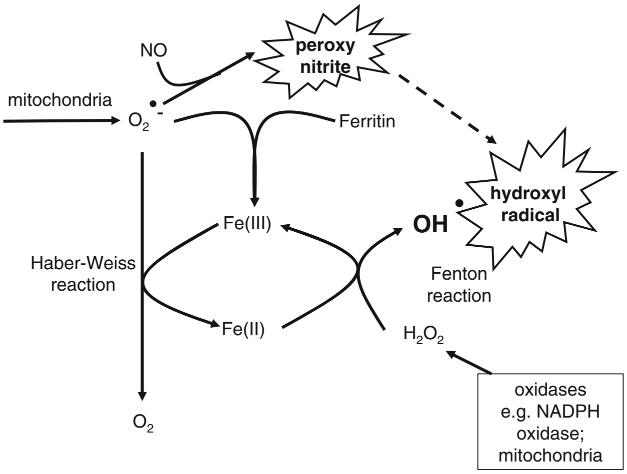
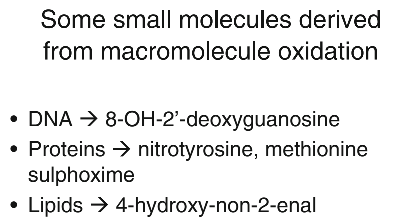


Fig. 1 The Haber-Weiss and Fenton reactions combine using poorly liganded iron in a **catalytic cycle** to produce the very damaging hydroxyl radical. Poorly liganded iron can also be liberated via the destruction of haem and other iron-containing substances. Peroxynitrite anion ($ONOO^{-}$) is produced by the reaction of superoxide and nitric oxide ($NO^{\bullet}$) which when protonated (pH ca 6.5–6.8) decomposes to $OH^{\bullet}$ and NO_2



Some small molecules derived from macromolecule oxidation

- DNA → 8-OH-2’-deoxyguanosine
- Proteins → nitrotyrosine, methionine sulphoxime
- Lipids → 4-hydroxy-non-2-enal

Fig. 2 Some small molecules that are derived from the oxidative attack of hydroxyl and other radicals on cellular macromolecules and that can act as biomarkers of oxidative stress, including that mediated by iron

O'Donnell and Freeman 2001) production or protein cysteine nitrosylation (Lancaster 2008; Landino 2008; Vaz and Augusto 2008) that can provide a means of their detection downstream. Some of these are shown in Fig. 2. A key point here is that despite the widespread and uncritical use of the term ROS to describe any 'Reactive Oxygen Species', most such as superoxide and peroxide are not terribly reactive, in contrast to the hydroxyl radical (and peroxynitrite) which is, and **unliganded iron is required for hydroxyl radical production in the Fenton reaction**. Hence the focus on unliganded iron rather than the more nebulous ROSs, albeit that (su)peroxide is necessarily involved.

Clearly the occurrence of these activities leads to the (more or less irreversible) formation of a variety of substances that can act as biomarkers of these activities (Kell 2009a), and such oxidised compounds are represented by both small and macro-molecules. For instance, 8-hydroxy-2′-deoxyguanosine (8-OHdG) (ChEBI 40304) also referred to as its tautomer 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) (HMDB03333) is produced when the hydroxyl radical reacts with DNA and damages it (e.g. Bal and Kasprzak 2002; Burrows and Muller 1998; Cooke et al. 2003, 2008; Lloyd et al. 1998; Loft and Poulsen 1996; Orhan et al. 2004; Shi et al. 2003; Toyokuni and Sagripanti 1996; Valavanidis et al. 2009; Valko et al. 2005), and **body-iron status correlates rather strongly with its production or urinary excretion** (Agarwal et al. 2004; Broedbaek et al. 2009; Fujita et al. 2007a, 2009; Gackowski et al. 2002; Hori et al. 2010; Kang et al. 1998; Kuo et al. 2008; Maruyama et al. 2007; Nakano et al. 2003; Toyokuni and Sagripanti 1996; Tuomainen et al. 2007; Valavanidis et al. 2005). The data in (Hori et al. 2010) relating urinary 8-OHdG levels to serum ferritin concentrations are particularly striking, and I have digitised them (cf. Pettifer et al. 2009 for pointers to automated ways of doing this in the future) and replotted some of them in Fig. 3.

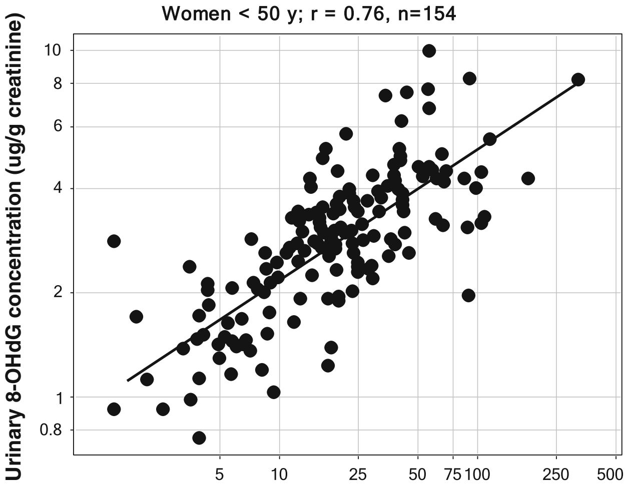


Fig. 3 Very strong relationship between serum ferritin concentrations and urinary concentrations of the DNA damage/oxidative stress marker 8-hydroxy-2′-deoxyguanosine. Data are replotted from Fig. 1 of Hori et al. (2010)

Ferritin levels (a common measure of body iron stores) are also widely associated with disease development/ severity/ poor outcomes (e.g. Alissa et al. 2007; Armand et al. 2007; Bartzokis et al. 2007; Braun et al. 2004; Bugianesi et al. 2004; Chen et al. 2006; Choi et al. 2005; Double et al. 2000; Fargion et al. 2001; Fernández-Real et al. 2002; Ford and Cogswell 1999; Forouhi et al. 2007; He et al. 2007; Hubel et al. 2004; Ishizaka et al. 2005; Jehn et al. 2004, 2007; Kaur et al. 2007; Kiechl et al. 1997; Lee et al. 2006f; Lim et al. 2001; Rayman et al. 2002; Rouault 2006; Salonen et al. 1992; Sheth and Brittenham 2000; Tuomainen et al. 1998; Valenti et al. 2007; Wilson et al. 2003; You et al. 2003; You and Wang 2005) (Adamkiewicz et al. 2009; Baune et al. 2010; Busca et al. 2010; DePalma et al. 2010; Ferrara et al. 2009; Ferrucci et al. 2010; Gamberini et al. 2008; Goodall et al. 2008; Inati et al. 2010; Kaysen 2009; Knovich et al. 2009; Kolberg et al. 2009; Lecube et al. 2008; Lim et al. 2010; Mateo-Gallego et al. 2010; McNeill et al. 2008; Menke et al. 2009; Qureshi et al. 2008; Rajpathak et al. 2009; Sharifi et al. 2008; Skinner et al. 2010; Song et al. 2009; Storey et al. 2009; Sun et al. 2008; Tsimikas et al. 2009; Valenti et al. 2010; Walker et al. 2010; Wang et al. 2010b; Yoneda et al. 2010; Zandman-Goddard and Shoenfeld 2008), though note that most assays are for the protein itself, and not for the full molecule including any iron that it may sequester effectively (Balla et al. 1992; Hintze and Theil 2006; Theil 2007) or otherwise.

Although iron is most commonly bivalent, Fe(II), or trivalent, Fe(III), this simple statement does not remotely cover the relevant chemistry and speciation that are necessary to recognise what forms of 'iron' may be safe and which are likely to catalyse damaging reactions. The first issue is that at neutral pH Fe(III) is more or less insoluble, and in aerobic environments it is necessary to chelate the otherwise 'free' Fe(III) with appropriate chelators or siderophores (especially for microbes, e.g. Andrews et al. 2003; Barry and Challis 2009; Cornelis and Andrews 2010; de Carvalho and Fernandes 2010; Haas et al. 2008; Johnson 2008; Miethke and Marahiel 2007; Raymond et al. 2003; Sandy and Butler 2009; Wandersman and Delepelaire 2004; Winkelmann 2002). These siderophores—secreted as are other bacterial pheromones (Kell et al. 1995)—typically have extremely tight binding constants ($K_\mathrm{f} > 10^{30}$, e.g. Clifton et al. 2009; Loomis and Raymond 1991) and can solubilise and sequester iron such that it can be internalised via suitable transporter molecules within the plasma membrane (Stintzi et al. 2000).

Iron contains up to six individual chelation sites, arranged octahedrally, and ligands can typically satisfy them partially (i.e. some ligands are bidentate or tridentate and need three or two molecules for full liganding/activity) or fully i.e. are hexadentate. **Since iron cannot be transmuted into any other substance, the only way to stop the damaging activity of free or partially liganded 'iron' is to ensure that *all of its six possible liganding sites are satisfied*, whether by endogenous chelators or those added from the diet or as pharmaceuticals**. Put another way, it is not simply enough to know that 'iron' is present at an adequate level but that it is available *in a suitably liganded form*. **Anaemia can be caused by poor liganding as well as by an actual shortage of 'iron' itself**. Note too that *partial* chelation in the presence of an antioxidant agent such as ascorbate (vitamin C) can in fact make ascorbate (or other reducing agent) act as a *pro*-oxidant and thus actually *promote* the production of $OH^{\bullet}$ radicals in the presence of inappropriately or inadequately liganded Fe(II) (Allen and Cornforth 2009; Fábián and Csordás 2003; Halliwell 2009; Hininger et al. 2005; Lachili et al. 2001; Long et al. 2000; Miller et al. 1990; Reif 1992; Sugihara et al. 1999). This very likely explains the often and indeed surprisingly disappointing clinical results obtained when using antioxidants alone (Bjelakovic et al. 2008; Giustarini et al. 2009; Kell 2009a; Miller et al. 2005).

The above facts are well known (e.g. Halliwell and Gutteridge 2006; Weinberg 2004), and I discussed them at length in a recent and wide-ranging review (Kell 2009a). My purpose here is to look more closely at the evidence that they are part of the sequelae of a number of predispositions to cellular and organismal death (whether by necrosis or apoptosis) that follow from a large variety of initial 'insults' or distal causes, whether of genetic or

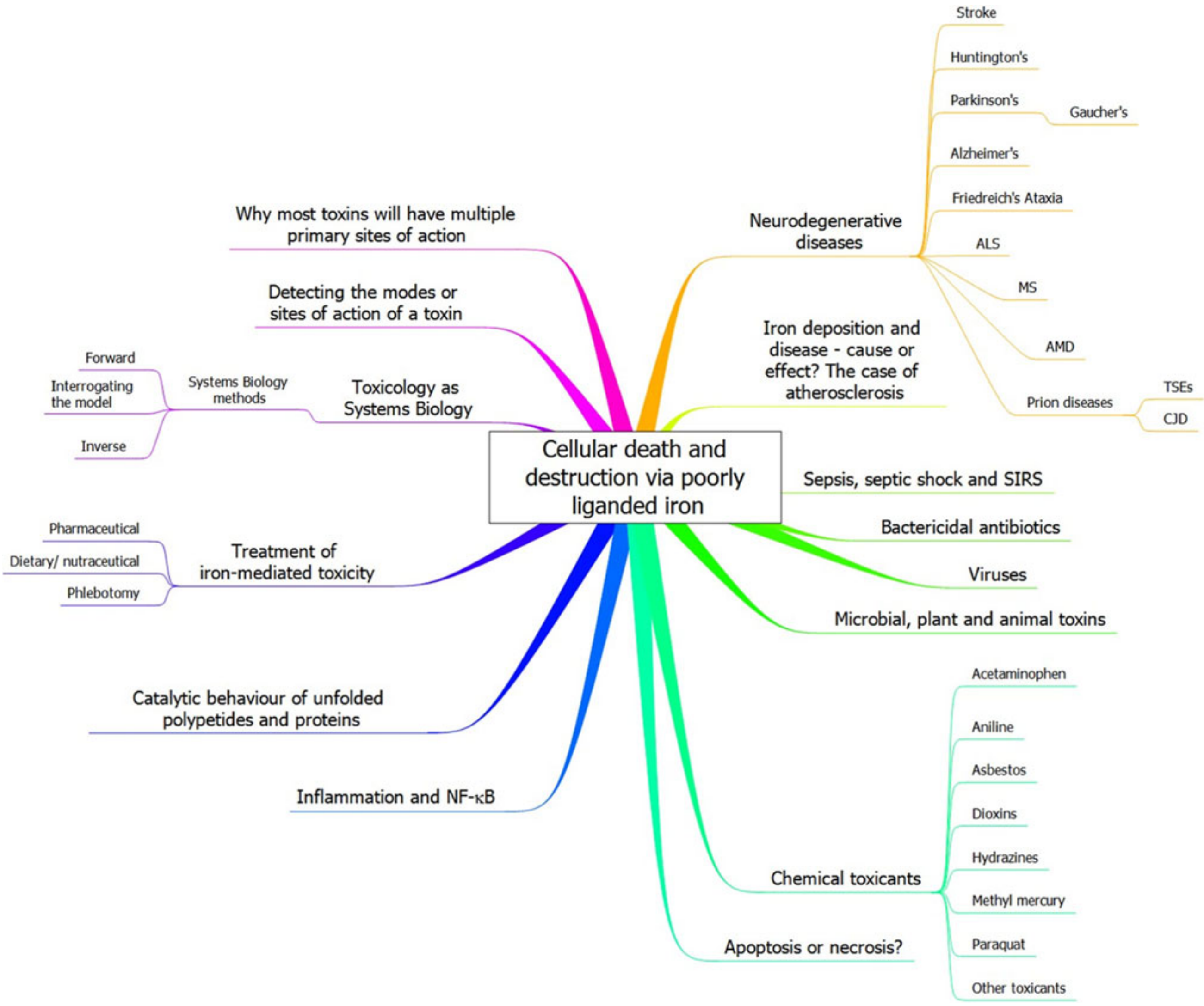


Fig. 4 A mind map (Buzan 2002) setting out the structure of this review. To read this start at "1 o'clock" and move outwards and clockwise

environmental origin (or both). While, as a systems property, many other cellular processes contribute measurably to any specific activity, **I suggest, in all the disparate cases I review, that it is the binding of poorly liganded iron (mainly bivalent) to inappropriate cellular structures that serves to generate this catalytic activity, albeit that the overall manifestations may differ at a physiological level, and I here review what evidence is available. This basic suggestion can be tested explicitly more or less easily.** I suggest further that it is this ongoing, autocatalytic activity based on positive feedback that is responsible for the really large-scale damage, leading to organismal death, that can occur in affected cells, tissues, organs and organisms. **This analysis also suggests an important role for iron chelation as part of combination approaches in the acute and chronic therapy of these conditions.** An overview of this article is given as a Mind Map (Buzan 2002) in Fig. 4.

Note that I do recognise that other transition and polyvalent metal ions (Al^{n+}, Cr^{n+}, Cu^{n+}, Mn^{n+}, Se^{n+}, Zn^{n+} etc.) may also contribute to the kinds of process I describe. However, for reasons of simplicity, focus, and because of the natural abundance of this metal in biological systems, it is 'iron' on which I shall concentrate. As previously (Kell 2009a), **I use the term 'iron' to include iron of any valencies or speciation**, unless specified otherwise.

Since the role of iron is obvious in cases of primary diseases of iron overload, such as hereditary haemochromatosis (e.g. Camaschella and Merlini 2005; Ellervik et al. 2007; Gan et al. 2010; Limdi and Crampton 2004; Mair and Weiss 2009; Marx 2002; McLaren and Gordeuk 2009; Pantopoulos 2008; Papanikolaou and Pantopoulos 2005; Pietrangelo 2006; Weiss 2010), thalassaemias (e.g. Borgna-Pignatti et al. 2005; Camaschella and Merlini 2005; Cao and Galanello 2010; Cohen et al. 2004; Gattermann 2009; Lam et al. 2008; Li et al. 2010; Mohkam et al. 2008; Peng et al. 2008; Taher et al. 2010; Vichinsky et al. 2005) and myelodysplastic syndrome (e.g. Cazzola et al. 2008; Cuijpers et al. 2010; Dreyfus 2008; Gattermann 2008; Greenberg 2006; Greenberg et al. 2008; Jabbour et al. 2009; Jädersten and Hellström-Lindberg 2010; Leitch 2007; Mahesh et al. 2008; Malcovati 2009; Porter et al. 2008; Wimazal et al. 2009), I largely ignore this literature. However, I recognise that the sequelae of iron overload, especially various kinds of organ failure, share many similarities to those I describe below, consistent with the role of iron in these other cases where its involvement has been less widely recognised. Clearly the commonality of any specific effect with those of known iron overload (Dever et al. 2010) might give strong hints for the involvement of iron in specific toxicological processes.

The literature survey at the time of initial submission for review extended to 14 June, 2010.

To start our survey, we look at the consequences of an acute cerebral infarction or stroke.

Stroke

Stroke is a term used to describe the destruction of brain cells, typically following a temporary blockage in blood flow (ischaemia-reperfusion injury) or an intra-cranial haemorrhage. The extent of damage varies considerably, and can be exacerbated because affected cells can release inflammatory cytokines that activate other cells in a similar way, providing a positive autocatalytic effect and leading to spreading of the damage. It is this secondary spreading that is especially damaging, but because it is slower (4–7days), it also affords the opportunity for therapeutic intervention (Qureshi et al. 2009). It is now clear that iron is intimately involved (Armengou and Davalos 2002; Bailey et al. 2006; Bishop and Robinson 2001; Chang et al. 2005; Dávalos, et al. 1994; Demougeot et al. 2004; Ferro and Dávalos 2006; Garoufi et al. 2006; Gillum et al. 1996; Lee et al. 2006e; Marniemi et al. 2005; Mascitelli and Pezzetta 2006; Mehta et al. 2004; Mu et al. 2005; Nakamura et al. 2006; Saxena et al. 2005; Selim and Ratan 2004; Switzer et al. 2006; Wagner et al. 2003; Wu et al. 2003; Zuliani et al. 2006; Adams 2007; Altamura et al. 2009; Assenza et al. 2009; Basak et al. 2008; Bosomtwi et al. 2008; Carbonell and Rama 2007; Cho et al. 2007; Ekblom et al. 2007; Hanson et al. 2009; Heckl 2007; Helal 2008; Jolkkonen et al. 2007; Justicia et al. 2008; Kaushal and Schlichter 2008; Kim et al. 2008a; Kobayashi et al. 2008; Lou et al. 2009; Maguire et al. 2007; Mazumdar et al. 2007; Mehdiratta et al. 2008; Millan et al. 2007, 2008; Millerot-Serrurot et al. 2008; Nighoghossian et al. 2008; O'Rourke et al. 2008; Ratan et al. 2008; Ross and Meschia 2009; Saleh et al. 2007; Santhosh et al. 2009; Verduzco and Nathan 2009; Walters and Rye 2009; Weng et al. 2008), whether by release from (ferritin in) cells or from the haem of haemoglobin. Iron chelators have thus shown promise in decreasing the sequelae of an initial stroke-inducing event (Demougeot et al. 2004; Ferro and Dávalos 2006; Hurn et al. 1995; Kompala et al. 1986; Mu et al. 2005; Patt et al. 1990; Prass et al. 2002; Selim and Ratan 2004; Soloniuk et al. 1992; White et al. 1988; Chen-Roetling et al. 2009; Gu et al. 2009; Hanson et al. 2009; Hua et al. 2008; Mazumdar et al. 2007; Méthy et al. 2008; Millerot-Serrurot et al. 2008; Mirre et al. 2010; Okauchi et al. 2009, 2010; Ratan et al. 2008; Robinson et al. 2009; Selim 2009; Verduzco and Nathan 2009), providing further evidence for the primary importance of iron in causing injury.

While stroke is a sudden occurrence, albeit with secondary consequences, a number of neurodegenerative diseases are rather more long term in their development, and we now look at several, each of which is seen to involve iron intimately.

Huntington's disease

The pathology of HD reveals striking neurodegeneration in the corpus striatum and shrinkage of the brain, leading to its most prominent manifestation, viz. movement disorders or chorea (Bhidayasiri and Truong 2004). Huntington's disease occurs via the addition of trinucleotide CAG repeats within exon 1 of the relevant gene, encoding (poly)glutamine (polyQ) repeats in the huntingtin protein (htt) and leading to a gain of (toxic) function (Bauer and Nukina 2009; Gusella and MacDonald 2000; Imarisio et al. 2008; Quintanilla and Johnson 2009). The number of these repeats determines both the time of onset of observable disease (more repeats meaning earlier onset) (Perutz and Windle 2001; Ross 1995; Walters and Murphy 2009), accounting for 70% of the variance (Imarisio et al. 2008), and the disease severity, implying that it is indeed the polyglutamines *themselves* that are the chief culprits. Some of the polyQ-containing huntingtin proteins can also aggregate to form inclusion bodies, and aggregation and neurodegeneration can in part be related (Chopra et al. 2007; Cowan et al. 2003; Michalik and Van Broeckhoven 2003; Nagai et al. 2003; Wang et al. 2005, 2009; Zhang et al. 2005a). Now the evidence for the involvement of poorly liganded iron in a wide variety of neurodegenerative diseases is overwhelming (e.g. Benarroch 2009; Bishop et al. 2010a; Brown 2009a; Friedman et al. 2007; Jellinger 1999; Ke and Qian 2003; Kell 2009a; Lee et al. 2006a; Perez and Franz 2010; Thompson et al. 2001; Youdim et al. 2004b; Zecca et al. 2004), and the question arises as to whether huntingtin (or, more likely, its degradation fragments), containing these polyQ tracts, can catalyse oxidative stress and/or hydroxyl formation directly. In an important paper, Firdaus et al. (Firdaus et al. 2006) show that that huntingtin inclusion bodies act as centres of oxidative stress and that partially purified inclusion bodies contain large amounts of oxidised proteins. Iron metabolism is deranged in gene knockdown models of Huntington's (Henshall et al. 2009; Lumsden et al. 2007), and experiments with the iron chelator deferroxamine revealed that the oxidation, localisation and structural organisation of the inclusion bodies formed by mutant htt were indeed irondependent. They did not demonstrate the ability of these inclusion bodies to catalyse hydroxyl formation, but this could easily be shown using specific assays, such as the hydroxylation of suitable aromatics (e.g. Grootveld and Halliwell 1986; Halliwell and Gutteridge 2006; Thomas et al. 2009a). The iron chelator clioquinol is also protective (Nguyen et al. 2005).

Parkinson's disease

Parkinson's disease (PD) results primarily from the death of dopaminergic neurons in the substantia nigra part of the brain and is characterised in particular by the presence of intracytoplasmic inclusions from protein aggregates called Lewy bodies (LB) and at the physiological level by a variety of movement disorders (e.g. Singh et al. 2007). It is strongly linked with oxidative stress (e.g. Alam et al. 1997; Büeler 2009; Jenner 2003; Jenner and Olanow 1996; Kidd 2000; Mandel et al. 2003; Olivares et al. 2009; Seet et al. 2010; Van Laar and Berman 2009; Zhang et al. 1999). Again (e.g. Berg et al. 2001; Bharath et al. 2002; Buchanan et al. 2002; Bush 2000; Castellani et al. 2002; Double et al. 2000; Good et al. 1998; Gotz et al. 2004; Hirsch and Faucheux 1998; Jellinger 1999; Johnson 2000; Olanow and Arendash 1994; Ostrerova-Golts et al. 2000; Sofic et al. 1991; Wolozin and Golts 2002; Altamura and Muckenthaler 2009; Andersen 2004; Barapatre et al. 2010; Baudrexel et al. 2010; Becker 2010; Becker et al. 2010a, b; Berg 2006, 2007; Berg and Hochstrasser 2006; Berg et al. 2006, 2008; Brar et al. 2009; Brown 2009b; Crichton and Ward 2006; Fasano et al. 2006; Friedman et al. 2007, 2009; Ghosh et al. 2010; Hirsch 2009; Jellinger 2009; Jimenez-Del-Rio et al. 2010; Kaur and Andersen 2004; Lee and Andersen 2010; Levenson 2003; Mandemakers et al. 2007; Matusch et al. 2010; Oakley et al. 2007; Salvador 2010; Shi et al. 2010; Wayne Martin 2009; Wypijewska et al. 2010; Yeager and Coleman 2010; Zecca et al. 2004; Zhang et al. 2005, 2010b)—there is overwhelming evidence for the involvement of iron in this neurodegeneration. Why these dopaminergic neurons are especially susceptible is not entirely clear, although dopamine is capable of reacting with iron directly to form a toxic complex (Arreguin et al. 2009; Paris et al. 2005) that probably itself catalyses hydroxyl formation. Iron chelators inhibit these inimical processes (Gal et al. 2006; Perez et al. 2008; Xu et al. 2008; Youdim et al. 2004a, b; Zheng et al. 2005), including (Kaur et al. 2003; Reznichenko et al. 2010; Youdim 2003) in the case of a Parkinson-like disease induced (Blum et al. 2001; Choi et al. 2009; Gal et al. 2009; Yokoyama et al. 2008) by 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) (ChEBI 17963). The Lewy bodies contain lipid and a variety of proteins, including ubiquitin, neurofilament, various proteasomal elements and α-synuclein, which may be oxidatively modified (Double et al. 2008). Ferric iron may itself catalyse the formation of α-synuclein oligomers (Brown 2009a; Hillmer et al. 2009; Peng et al. 2010), and copper may also be involved (Wang et al. 2010c).

Melanins are polymers of polyphenols, especially of L-dopamine, although neuromelanin, which also contains oxidatively polymerised dopamine or noradrenaline with the possible involvement of cysteinylderivatives (Fedorow et al. 2005), is of special interest here. The substantia nigra also contains a substantial amount of the dark, insoluble polymeric pigment neuromelanin, and this has been shown directly to bind (and release) iron in high amounts (Double et al. 2003a, b; Fasano et al. 2006; Faucheux et al. 2003; Gerlach et al. 2003, 2008; Shamoto-Nagai et al. 2006), and thereby to produce an iron-loaded form that seems to serve as a reservoir catalysing (hydroxyl) radical formation and whose amounts correlate with PD. In this case, the in vitro experiments have been done, and incubation of human neuromelanin with iron in vitro stimulates oxidative tissue damage (Ben-Shachar et al. 1991; Double et al. 2003a; Gerlach et al. 2008).

Another dark pigment commonly observed in PD patients (and other neurodegenerative diseases) is lipofuscin (Double et al. 2008; Jung et al. 2007; Terman and Brunk 2004). Lipofuscin too consists of lipids and oxidised proteins, often crosslinked by oxidised lipid derivatives such as (E)-4-hydroxy-non-2-enal (ChEBI 58968) and can adsorb high contents of metals (including iron) of up to 2% by weight (Jung et al. 2007). It is typically formed in lysosomes from degrading mitochondria (Terman et al. 2006a), themselves rich in metalloproteins, and the inability of cells to degrade it means that (purportedly) non-dividing cells (such as brain tissue) simply accumulate it as cells age (Terman and Brunk 2004, 2006). This arguably explains why non- or rarely-dividing tissues such as brain tissues are particularly susceptible, though note the important and increasing evidence (e.g. Abrous et al. 2005; Christie and Cameron 2006; Demir et al. 2009; Fuchs and Gould 2000; Götz and Huttner 2005; Gould 2007; Imayoshi et al. 2009; Leuner et al. 2007; Lledo et al. 2006; Ohnuma and Harris 2003; Taupin 2007; Zhao et al. 2008) for considerable turnover—neurogenesis—in at least some regions of the brain. The **autocatalytic nature** of the process—lipofuscin loaded with iron catalyses more lipofuscin production—is especially dangerous and can (as one would predict) be inhibited using appropriate iron chelators (Persson et al. 2003). Iron chelation also assists neurogenesis (Nowicki et al. 2009).

Thus, as with Huntington's, Parkinson's disease is clearly characterised by all the hallmarks of hyperactive hydroxyl radical generation, leading to cell death and destruction, in this case mainly, it would seem (Chen et al. 2007; Chiueh et al. 2000; Ekshyyan and Aw 2004; Jellinger 2002; Jenner 2003; Jenner and Olanow 1996; Kermer et al. 2004; Levenson 2005; Loh et al. 2006; Mandel et al. 2005; Mattson 2006; Okouchi et al. 2007; Xu et al. 2008a; Yasuda and Mochizuki 2010), by apoptosis.

Gaucher's disease

Gaucher's disease is an autosomally recessive inborn error of metabolism due to deficiency of a lysosomal enzyme, glucocerebrosidase (GBA), resulting in the accumulation of glucocerebroside in large macrophages throughout the reticuloendothelial system, leading to various neuronopathies. Given that the lysosome is the site of most labile iron in the cell (Fakih et al. 2008; Gorria et al. 2008; Kurz et al. 2004, 2008a, b; Persson 2005; Tenopoulou et al. 2007; Terman et al. 2006b; Yu et al. 2003), it is also of interest that there is an increased frequency of mutations in the gene encoding GBA among patients with Parkinson's disease (e.g. Aharon-Peretz et al. 2004; Clark et al. 2007; Gan-Or et al. 2008; Lwin et al. 2004), and vice versa (Sidransky et al. 2009). Iron dysregulation is also well established in Gaucher's disease (Finch et al. 1986; Lee et al. 1967, 1977; Lorber 1960, 1970; Morgan et al. 1983; Schiano et al. 1993; Weisberger et al. 2004). This recognition of the role of iron dysregulation in Gaucher's disease may offer novel therapeutic approaches.

Alzheimer's disease

Alzheimer's disease (AD), the commonest of the neurodegenerative disease of ageing, shares many similarities with Huntington's and Parkinson's diseases, not least the extensive evidence for the role of oxidative stress (e.g. Butterfield et al. 2007; Christen 2000; DiMauro and Schon 2008; Good et al. 1996; Milton 2004; Miranda et al. 2000; Moreira et al. 2009; Nunomura et al. 2001, 2006; Reddy and Beal 2008; Reddy et al. 2009; Rottkamp et al. 2000; Smith et al. 1996, 2000; Zhu et al. 2007) and of iron (e.g. Adlard and Bush 2006; Avramovich-Tirosh et al. 2007a; Becker et al. 2010b; Bishop et al. 2002; Blázquez et al. 2007; Bolognin et al. 2009b; Brar et al. 2009; Bush 2000, 2003, 2008; Casadesus et al. 2004; Castellani et al. 2007; Collingwood and Dobson 2006; Collingwood et al. 2008; Connor and Lee 2006; Ding et al. 2009; Doraiswamy and Finefrock 2004; Gerlach et al. 1994; Good et al. 1996; Hegde et al. 2009; Honda et al. 2004; Jellinger et al. 1990; Jellinger 2009; Kala et al. 1996; Lehmann et al. 2006; LeVine 1997; Lovell et al. 1998; Malecki and Connor 2002; Mandel et al. 2007; Markesbery 1997; Markesbery and Lovell 1998; Mascitelli et al. 2009; Olanow and Arendash 1994; Ong and Farooqui 2005; Quintana et al. 2006; Rival et al. 2009; Robson et al. 2004; Silvestri and Camaschella 2008; Smith et al. 1997a, 2010; Tabner et al. 2005; Thomas and Jankovic 2004; Thompson et al. 2001; Valko et al. 2005; Zatta et al. 2009; Zecca et al. 2004; Zheng et al. 2005). It is especially noteworthy that iron correlates with disease severity as measured by cognitive ability (Ding et al. 2009; Gómez Ravetti et al. 2010; Grossi et al. 2009; Lavados et al. 2008; Perez et al. 2010; Smith et al. 2010). AD is characterized by the loss of neurons in the cognitive centres of the brain and by the presence of two separate pathological lesions, extracellular β-amyloid (Aβ) plaques (e.g. Dong et al. 2003; Scott and Orvig 2009) and neurofibrillary tangles within neurons (Shcherbatykh and Carpenter 2007).

Again, there is evidence that insoluble polymers (fibrillary tangles) of proteins such as the β-amyloid can bind iron (Castellani et al. 2007; Dickens and Franz 2010; Exley 2006; Good et al. 1992; Jiang et al. 2009; Mancino et al. 2009; Rival et al. 2009; Sayre et al. 2000b; Smith et al. 2007) and thereby act in an autocatalytic manner to promote further radical production and oxidative stress. There is a also relationship between the ability to bind haem and neurotoxicity (Atamna 2009; Atamna et al. 2009), and (HFE) mutations that cause haemochromatosis increase the susceptibility to AD (Bartzokis et al. 2010; Candore et al. 2003; Combarros et al. 2003; Connor and Lee 2006; Haacke et al. 2005; Kauwe et al. 2010; Lleó et al. 2002; Moalem et al. 2000; Pulliam et al. 2003; Robson et al. 2004; Sampietro et al. 2001), especially when in the presence of the APOE4 allele (Pulliam et al. 2003). (HFE mutations also increase susceptibility to PD (Biasiotto et al. 2008; Dekker et al. 2003)—but cf. (Aamodt et al. 2007)—and to ALS (Ellervik et al. 2007)).

Importantly, iron chelators have been shown to ameliorate the development of fibril formation/neurodegeneration/dementia/AD (Amit et al. 2008; Avramovich-Tirosh et al. 2007a; Bandyopadhyay et al. 2006; Barnham et al. 2004; Biran et al. 2009; Bolognin et al. 2009a; Crapper McLachlan et al. 1991; Cuajungco et al. 2000; Faux et al. 2010; Finefrock et al. 2003; Liu et al. 2009b, c, 2010; Mancino et al. 2009; Mandel 2007, 2008; Reznichenko et al. 2006; Scott and Orvig 2009; Weinreb et al. 2009a; Zheng et al. 2005). Although this fact rarely appears in papers setting out therapeutic options for preventing (or at least ameliorating the progress of) AD, this already considerable literature suggests that trials using modern iron chelators would be of worth.

Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease)

ALS is another neurodegenerative disease in which iron has been strongly implicated (and thus the same kinds of mechanism as described previously) (Bush 2000; Carri et al. 2003; Cozzolino et al. 2008; Goodall et al. 2008; Jeong et al. 2009; Kasarskis et al. 1995; Mattson 2004; Migliore et al. 2005; Molfino et al. 2009; Qureshi et al. 2008; Reynolds et al. 2007; Sadrzadeh and Saffari 2004; Sayre et al. 2000a; Scott and Orvig 2009; Spasojević et al. 2010; Sutedja et al. 2007; Wang et al. 2004). Again, the clear benefits of iron chelators in mouse models (Jeong et al. 2009; Petri et al. 2007) and elsewhere (Avramovich-Tirosh et al. 2007b; Bolognin et al. 2009a) would seem to merit trials in humans known to be at risk. Long-standing associations of some forms of ALS with mutations in genes coding for superoxide dismutase 1 (e.g. Dalle-Donne 2007; Pasinelli and Brown 2006; Rosen et al. 1993; Vucic and Kiernan 2009; Wijesekera and Leigh 2009) are consistent with this, and recent genetic associations (e.g. Kwiatkowski Jr. et al. 2009; Valdmanis et al. 2009; Vance et al. 2009) include one with optineurin (Maruyama et al. 2010) that together with other evidence implies an interaction with NF-κB (see later) leading to the downstream effects of apoptotic neuronal cell death.

Friedreich's ataxia

Friedreich's ataxia is another neurodegenerative disease caused by the insertion of a trinucleotide repeat (or occasionally a missense mutation) in the gene encoding a protein called frataxin (Adibhatla and Hatcher 2010; Babady et al. 2007; Becker and Richardson 2001; Bencze et al. 2006; Chakravarty 2003; González-Cabo et al. 2009; Palau 2001; Pandolfo 2009; Patel and Isaya 2001; Puccio 2009; Rötig et al. 2002; Santos et al. 2010; Sheftel et al. 2010). Driven not least by studies in bacteria and lower eukaryotes (Ayala-Castro et al. 2008; Becker and Richardson 2001; Bulteau et al. 2007; Cavadini et al. 2000; Cook et al. 2006; De Freitas et al. 2003; Foury 1997; Foury and Cazzalini 1997; Foury and Talibi 2001; González-Cabo et al. 2005; Irazusta et al. 2006, 2008; Knight et al. 1999; Pastore et al. 2007; Vázquez-Manrique et al. 2006; Wang and Craig 2008; cf. Seguin, et al. 2010), it is now understood that frataxin is a mitochondrial iron chaperone protein (Atkinson and Winge 2009; Ba et al. 2009; Babady et al. 2007; Bencze et al. 2007; Cavadini et al. 2002; Correia et al. 2008; Gakh et al. 2006; Haugen et al. 2010; Huang et al. 2008a; Huang et al. 2009; Karlberg et al. 2006; Kondapalli et al. 2008; Lill 2009; Lill and Muhlenhoff 2008; Lu and Cortopassi 2007; MacKenzie et al. 2008; Mandemakers et al. 2007; Marmolino and Acquaviva 2009; Napier et al. 2005; Napoli et al. 2006; O'Neill et al. 2005; Pandolfo 2009; Pandolfo and Pastore 2009; Pastore et al. 2007; Reddy 2008; Schagerlöf et al. 2008; Sparaco et al. 2009; Wilson 2006; Zanella et al. 2008) involved in the safe insertion of Fe(II) during the production of Fe–S centres in the mitochondrial respiratory chain (Anderson et al. 2005). The defect thus leads to the liberation of mitochondrial iron (Huang et al. 2009; Popescu et al. 2007; Richardson et al. 2009a). Fenton chemistry is strongly implicated (Park et al. 2002; Sturm et al. 2005), as the attenuation of H_2O_2 production (but not of superoxide) (Anderson et al. 2005) ameliorates the disease (Anderson et al. 2008). As would be expected, appropriate iron chelation may have therapeutic benefits (Boddaert et al. 2007; Campanella et al. 2009; Goncalves et al. 2008; Kakhlon et al. 2010; Lim et al. 2008; Marmolino and Acquaviva 2009; Santos et al. 2010; Schulz et al. 2009; Sohn et al. 2008). This very clear molecular picture underlines strongly the problems of iron release leading to cell death and destruction.

Multiple sclerosis

MS is an inflammatory demyelinating autoimmune disease affecting the CNS. While its underlying causes remain uncertain, and do not seem to have a significant genetic component (Baranzini et al. 2010; Oksenberg et al. 2008; Ramagopalan et al. 2008), ROS are certainly implicated (Adibhatla and Hatcher 2010), and antioxidant therapies may be useful (Mirshafiey and Mohsenzadegan 2009). It is at least plausible that part of the demyelination is caused by ROS and in particular hydroxyl radicals, and it is thus of much interest that iron dysregulation and/or deposition have indeed been implicated directly (Adams 1988; Bakshi et al. 2000, 2001, 2002, 2008; Bermel et al. 2005; Brass et al. 2006a, b; Ceccarelli et al. 2009, 2010; Chard and Miller 2009; Craelius et al. 1982; Drayer et al. 1987; Eissa et al. 2009; Exley et al. 2006; Filippi and Agosta 2009; Ge et al. 2007; Grimaud et al. 1995; Haacke et al. 2005, 2009, 2010; Hammond et al. 2008; He and Yablonskiy 2009; Khalil et al. 2009; LeVine and Chakrabarty 2004; Neema et al. 2007a, b, 2009a, b; Pirko et al. 2009; Sayre et al. 2005; Schenck and Zimmerman 2004; Simka and Rybak 2008; Singh and Zamboni 2009; Stankiewicz et al. 2007; Tjoa et al. 2005; Walter et al. 2009; Zamboni 2006; Zivadinov and Bakshi 2004; Zivadinov and Minagar 2009). While the extent of causality of the iron dysregulation in MS is not yet established, it is highly pertinent that iron chelators have been shown to suppress disease progression in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (Bowern et al. 1984; Mitchell et al. 2007; Pedchenko and LeVine 1998). To say the least, the question of the involvement of iron in the human disease would seem to need pursuing with some urgency.

Age-related macular degeneration

While this review is intended to be much more circumscribed than the previous one (Kell 2009a), there are some pertinent diseases in which my understanding has improved significantly, and age-related macular degeneration is one such. Age-related macular degeneration (AMD) (Rattner and Nathans 2006) is recognised as the leading cause of blindness and visual disability in the elderly in developed countries (Fine 2005; Harvey 2003; Lotery and Trump 2007; Tielsch et al. 1995). Interestingly, despite the relatively modest impact of genome-wide association studies to date (Maher 2008; Moore et al. 2010), and notwithstanding their promise as their statistical power improves, 80% of the variation in susceptibility to AMD is said to be explainable (Collins 2010) (and see e.g. Chu et al. 2008) though cf. e.g. (Chen et al. 2010; Hadley et al. 2010; Katta et al. 2009; Neale et al. 2010; Patel et al. 2008; Sobrin et al. 2010) by just two genes concerned with inflammation combined with two environmental factors (smoking and obesity). The environmental factors can certainly be related to iron dysregulation. Indeed, as previously discussed, iron is significantly implicated in AMD (and other related diseases such as glaucoma) (Blasiak et al. 2009; Cai et al. 2000; Charkoudian et al. 2008; Chen et al. 2009; Chowers et al. 2006; Dentchev et al. 2005; Dunaief 2006; García-Castiñeiras 2010; Goralska et al. 2009a, b, c; Hahn et al. 2003, 2004; He et al. 2007; Loh et al. 2009; Richer et al. 2002; Wong et al. 2007), iron chelation may help to reverse the process (Voloboueva et al. 2007), and dietary and other antioxidants are also protective (see Tan et al. 2008; Wang et al. 2009).

Prion diseases: including transmissible spongiform encephalopathies and Creutzfeldt–Jakob disease

A particularly striking set of diseases, where the downstream events manifest as extreme cellular destruction leading to large areas of (brain) tissue disappearing completely, are represented by the prion diseases, in particular the TSEs including bovine spongiform encephalopathy (BSE) (e.g. Aguzzi et al. 2008a; Aguzzi and Heikenwälder 2006; Caughey and Baron 2006; Caughey and Lansbury 2003; Linden et al. 2008) and scrapie (e.g. Bulgin and Melson 2007; Hur et al. 2002; Roostaee et al. 2010; Wisniewski and Sigurdsson 2007), kuru (Gajdusek 2008; McLean 2008) and CJD (e.g. McLean 2008; Peden and Ironside 2004) (note too the co-location of amyloid plaques and spongiform degeneration in CJD, Ghoshal et al. 2009).

Now it is well known that prion diseases are caused in part (or at least accompanied by) the conversion of the prion protein PrP from its normal form $\mathrm{PrP}^{\mathrm{C}}$ to a conformationally distinct version $\mathrm{PrP}^{\mathrm{Sc}}$ and that the latter can autocatalyse this conversion (Aguzzi and Heikenwälder 2006; Aguzzi et al. 2008b; Prusiner 1998, 2001; Tamgüney et al. 2008; Watts and Westaway 2007). However, $\mathrm{PrP}^{\mathrm{Sc}}$ levels are in many cases poorly correlated with prion disease progression, suggesting that it is necessary but not sufficient; ‘something else’ is required (Caughey and Baron 2006). Equally, it is far from clear how a simple conformational change of a protein leads to the vacuolation or spongiosis (e.g. Aguzzi 2006; Aguzzi et al. 2007; Armstrong et al. 2001; Chung et al. 1999; Crozet et al. 2008; Diedrich et al. 1991; Foster et al. 2001; Julius et al. 2008; Kourie 2002; Mallucci et al. 2003; Mallucci et al. 2007; Miele et al. 2001; Sakudo and Ikuta 2009a, b; Westaway et al. 1994; Williams et al. 1997) (formation of holes) in brain tissue characteristic of late-stage prion disease (and indeed of Alzheimer's (Erkinjuntti et al. 1996; Sakudo and Ikuta 2009a). The question then arises as to whether it is possible that PrP^{Sc} modifies iron metabolism in an unfavourable way (and/or vice versa), not least since prion proteins bear phylogenetic relationships to the ZIP family of metal ion transporters (Schmitt-Ulms et al. 2009). Building on earlier work relating prion biology with (especially) iron-induced oxidative stress (e.g. Bareggi et al. 2009; Barnham et al. 2006; Basu et al. 2007; Choi et al. 2006; Fernaeus et al. 2005a, b; Fernaeus and Land 2005; Iwamaru et al. 2008; Kim et al. 2000, 2001, 2007; Lee et al. 2007; Lehmann 2002; Milhavet and Lehmann 2002; Pamplona et al. 2008; Park et al. 2008; Petersen et al. 2005; Pollera et al. 2005; Rana et al. 2009; Stegmann and Grohmann 2003; Westergard et al. 2007; Wong et al. 2001), this is exactly what Singh and colleagues (Singh et al. 2009a, b, c, 2010a, b) have now demonstrated, which is that the 'something else' (Kell 2009a, b) is (as so often) an imbalance in iron metabolism. They start by showing (Singh et al. 2009c) that even normal PrP^{C} mediates cellular iron uptake and transport and that mutant PrP forms alter cellular iron levels differentially.

PrP^{C} binds iron tightly, and this helps effect its conversion to PrP^{Sc} (Singh et al. 2010a, b). Singh et al. (2009a) showed that PrP^{Sc} can sequester cellular iron in insoluble PrP^{Sc}–ferritin complexes, making it bio-unavailable, and that this leads to an upregulation of iron uptake via transferrin and its receptor, leading to an overall iron excess in brain tissue. This was true for both scrapie and sporadic Creutzfeldt–Jakob disease, and stresses that it is not only the total amount of Fe(II) and Fe(III) that matter but their *speciation*. Mice knocked out for PrP also show derangement in iron metabolism (Singh et al. 2009b), and given what we know already (Kell 2009a) this leads to many obvious predictions of other diseases (Altamura and Muckenthaler 2009; Granic et al. 2009; Reddy et al. 2009; Serra et al. 2009) to which they might be susceptible. It has not yet been shown that PrP^{Sc}–ferritin complexes catalyse $OH^{\bullet}$ production directly, but if this is increased in diseased brains this continuous, *autocatalytic* spewing out of toxic $OH^{\bullet}$ radicals would clearly be able to account for the massive damage observed. A systems biology approach by Hwang et al. (Hwang et al. 2009) also found many genes of iron metabolism modified in prion disease. There is little doubt that all these new findings about the role of iron (and other metals, e.g. Brown et al. 1997) open up many new inroads into understanding the important role of iron in prion diseases, and thereby novel therapeutic options involving both anti-oxidants and cell-permeable iron chelators. Some of these new ideas and findings are illustrated in Fig. 5.

Finally, here, it is worth pointing up the evidence for the role of iron and its metabolic dysregulation in the oxidative stress-mediated aetiology of scrapie (Choi et al. 2006; Fernaeus et al. 2005a; Fernaeus and Land 2005; Gudmundsdóttir et al. 2006; Kim et al. 2000, 2007; Pamplona et al. 2008; Singh et al. 2009a, 2010a, b; Wong et al. 2001a, b; Yun et al. 2006), a prion disease of sheep and goats (Bulgin and Melson 2007; Hur et al. 2002) and of CJD (Choi et al. 2006; Freixes et al. 2006; Petersen et al. 2005; Singh et al. 2009a, 2010a, b). As such, the use of geostatistics relating the variation of metals present in soils to prion disease prevalence is also a powerful tool here (e.g. Gudmundsdóttir et al. 2006; Imrie et al. 2009; Purdey 2000; Stevens et al. 2009).

Iron deposition and disease: cause or effect? The case of atherosclerosis

I have implied that the role of unliganded iron is *causative* of a variety of sequelae, but sometimes this is hard to infer as the networks in which iron is involved are multiple and complex (hence the need for a systems approach—see later), and often simple one-time snapshots of covariates do not permit the inference of causality. However, one effect of the reaction of hydroxyl radicals (their formation catalysed by unliganded iron) with proteins (or lipids) is to tend to make those proteins (or lipids) insoluble or fibrotic (Davies 2005; Fig. 6), and if one believes that this *is*

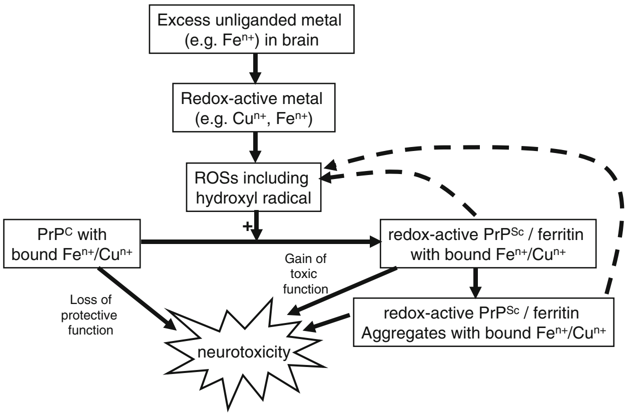


Fig. 5 Some of the interactions between the prion protein in its two main conformations, reactive oxygen species and iron dysregulation. This diagram is based on Fig. 12 of (Singh et al. 2010b), and illustrates in particular the autocatalytic nature of the ROS- and iron-dependent conversion of PrP^{C} to PrP^{Sc} and the neurotoxicity of the latter

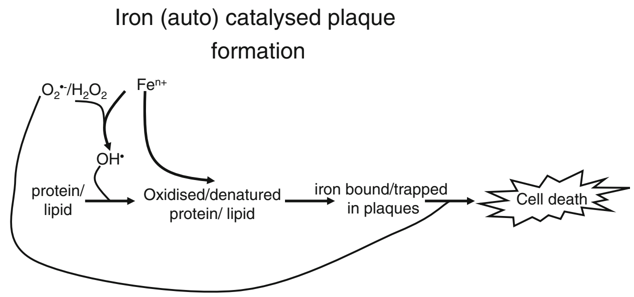


Fig. 6 Iron catalyses the formation of the hydroxyl radical (and thence other kinds of ROS) that can react with proteins and lipids to denature them, leading to insoluble plaques and other fibrotic structures that can themselves bind/entrap the iron that caused their formation. This bound iron can cause further hydroxyl radical formation such that the process is autocatalytic. Eventually this overwhelms cellular defences, leading to cell death (with further release of iron)

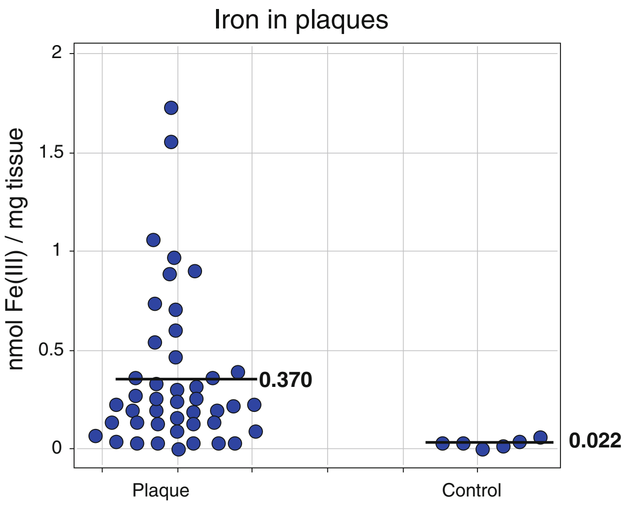


Fig. 7 Large (17-fold) accumulation of EPR-detectable iron in atherosclerotic plaques relative to healthy non-atherosclerotic ('intima') controls. The difference is highly significant (P = 0.0001). Data are replotted from those in Fig. 1b of Stadler et al. (2004)

causative, the presence of insoluble plaques should correlate with the presence of the iron that is seen to have caused their formation and thereby became entrapped (and may yet be further reactive). Because of its biomedical importance, considerable work has been performed on atherosclerotic lesions, which provide a very clear example.

Atherosclerosis is a progressive (and inflammatory) disease (Altman 2003; Binder et al. 2002; Blake and Ridker 2001; Duewell et al. 2010; Dwyer et al. 2004; Forrester 2002, 2004; Gieseg et al. 2009; Grainger 2007; Hansson 2001, 2005; Himmelfarb et al. 2002; Kibel et al. 2008; Kunsch and Medford 1999; Libby 2002; Libby et al. 2002; Madamanchi et al. 2005a, b; Mullenix et al. 2005; Nigro et al. 2006; Packard and Libby 2008; Paoletti et al. 2004; Popa et al. 2007; Rader and Daugherty 2008; Ridker et al.et al. 2004; Ross 1999; Schleicher and Friess 2007; Subramanian and Ferrante 2009; Sullivan 2009; Tan and Lip 2008; Tang et al. 2009; Taqueti et al. 2006; Tedgui and Mallat 2006; van Leuven et al. 2008; van Oostrom et al. 2004; Willerson and Ridker 2004; Young et al. 2002) characterized by the accumulation of both oxidised lipids and various fibrous elements in arteries, often as plaques (Lusis 2000; Stocker and Keaney 2004). Several lines of evidence point to the involvement of iron in these processes:

- Both iron and oxidised lipids (de Valk and Marx 1999; Smith et al. 1992) are found in atherosclerotic lesions (Altamura and Muckenthaler 2009; Brewer 2007; Chau 2000; Fernandes de Godoy et al. 2007; Gajda et al. 2008; Halliwell 2009; Horwitz et al. 1998; Kazi et al. 2008; Lee et al. 1998; McRae et al. 2009; Rajendran et al. 2007; Ramakrishna et al. 2003; Roijers et al. 2005; Smith et al. 1992; Stadler et al. 2004; Stanley et al. 2006; Stocker and Keaney 2005; Sullivan 2009; Watt et al. 2006; Wolff et al. 2004; Yuan and Li 2008)
- Iron depletion by dietary or other means delays the formation of such lesions (Ferrara and Taylor 2005; Halliwell 2009; Lee et al. 1999; Matthews et al. 1997; Ponraj et al. 1999; Ren et al. 2005).
- There is a correlation between iron status and atherosclerosis (Ahluwalia et al. 2010; Chau 2000; Day et al. 2003; de Valk and Marx 1999; DePalma et al. 2010; Gozzelino et al. 2010; Howes et al. 2000; Kallianpur 2005; Kartikasari et al. 2009; Kiechl et al. 1997; Lapenna et al. 2007; Marx et al. 2008; McRae et al. 2009; Minqin et al. 2003; Ramakrishna et al. 2003; Ren et al. 2003; Salonen et al. 1992; Shah and Alam 2003; Sullivan 2007, 2009; You et al. 2003; You and Wang 2005; Zacharski et al. 2000; Zacharski and Gerhard 2003) (and zinc is protective only against subsequent calcification, Stadler et al. 2008)
- Exogenous ferric iron is deleterious to endothelial function (Rooyakkers et al. 2002)
- Iron chelation improves endothelial function (Altamura and Muckenthaler 2009; Duffy et al. 2001; Halliwell 2009; Ishizaka et al. 2005; Saito et al. 2005; Thomas et al. 2006).
- Iron levels in plaques correlate with the amount of oxidised proteins therein (Stanley et al. 2006); indeed in one study (Stadler et al. 2004), the EPR-detectable iron (essentially Fe(III)) in atherosclerotic tissue was *seventeen times greater* than that in the equivalent healthy tissue. I redraw these data in Fig. 7.

It seems clear that the application of similar studies to other diseases in which plaque formation occurs will be of benefit. Indeed, the location of iron in plaques has also been observed, for instance, for Alzheimer's (e.g. Collingwood et al. 2008; Connor et al. 1992; El Tannir El Tayara et al. 2006; Ghribi et al. 2006; Haacke et al. 2005; Lovell et al. 1998; Morgan et al. 2004; Quintana 2007; Quintana et al. 2006; Sayre et al. 2000b; Schrag et al. 2009), ALS (Leveugle et al. 1997), MS (Haacke et al. 2009) and Parkinson's (see above).

Sepsis, septic shock and the systemic inflammatory response syndrome

Although prions lack nucleic acids, they are seen as infectious agents. Bacteria are more conventional infective agents, and bacterial sepsis provides a very interesting example in which iron release is the key to cell death and the multiple organ failure that normally precedes organismal death. This said, the processes leading to septic shock and ultimately death (Fig. 8) are independent of the presence of viable/culturable bacteria (as defined in Kaprelyants et al. 1993; Kell et al. 1998), i.e. in the apparent absence of infection (Goris 1990; Suntharalingam et al. 2006). This is because it is the *products* of bacteria, especially lipopolysaccharide (LPS), that cause the cells themselves to initiate the progressive processes of self-destruction. The sequelae are typically referred to as a systemic inflammatory response syndrome (SIRS) (e.g. Baue et al. 1998; Beal and Cerra 1994; Bolton 1996; Bone 1996; Davies and Hagen 1997; Gutteridge and Mitchell 1999; Hotchkiss and Karl 2003; Johnson and Mayers 2001; Keel and Trentz 2005; Leithead et al. 2009; Lolis and Bucala 2003; Martin et al. 2003; Nguyen et al. 2006; Protti and Singer 2006; Rittirsch et al. 2008; Ulloa et al. 2009).

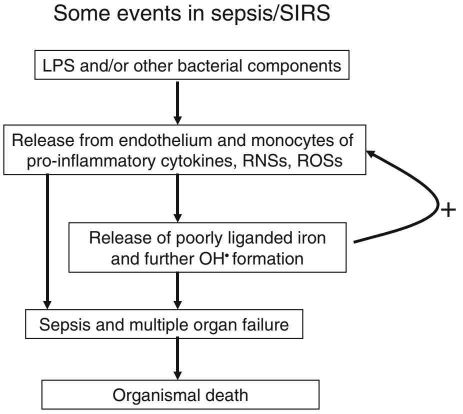


Fig. 8 The major events accompanying sepsis and the Systemic Inflammatory Response Syndrome. Note in particular the positive feedback by which the release of pro-inflammatory cytokines and ROSs leads to the release of poorly liganded iron (e.g. from ferritin and haem) that causes the release of further inflammatory cytokines and ROSs. In principle, iron chelators could interfere with this vicious cycle

It is by now well established that—while a 'cytokine storm' (Huang et al. 2005; Sriskandan and Altmann 2008; Stacey et al. 2009; Suntharalingam et al. 2006; Wang and Ma 2008; Woo et al. 2010) is an important part of the aetiology of sepsis/septic shock—these phenomena are associated with the hyperproduction of ROSs (Abdelrahman et al. 2005; Andrades et al. 2005; Bulger and Maier 2001; Cadenas and Cadenas 2002; Closa and Folch-Puy 2004; Crimi et al. 2006a, b; Goode and Webster 1993; Gutteridge and Mitchell 1999; Horn 1998; Javadi et al. 2005; Lagan et al. 2008; Lemineur et al. 2006; Mishra 2007; Protti and Singer 2006; Quinlan et al. 2001; Redl et al. 1993; Victor et al. 2004, 2005; Vlessis et al. 1995), and (local and circulating) free iron is raised in sepsis and related conditions (Duvigneau et al. 2008; Galley et al. 1996, 1997; Galley and Webster 1996; Ghio et al. 2003; Lagan et al. 2008), as is the iron siderophore-binding protein lipocalin-2 (Hattori et al. 2009).

The natural iron-chelating antioxidant melatonin has been found to be particularly effective in preventing septic shock (Carrillo-Vico et al. 2005; Escames et al. 2006; Reynolds et al. 2003), and a variety of suitable antioxidants have shown promise (Bekyarova et al. 2009; Cuzzocrea et al. 2001, 2004; Di Paola et al. 2006; Galley et al. 1997; Mishra 2007; Nathens et al. 2002; Sebai et al. 2009; Streck et al. 2008; Zapelini et al. 2008). Most importantly, antioxidants are especially effective when given in combination with iron chelators (Barichello et al. 2007; Ritter et al. 2004, 2006) (see also Bulucu et al. 2009; Cassol et al. 2009; Petronilho et al. 2009; Pinho et al. 2005; Teixeira et al. 2008; Valvassori et al. 2008). Erythropoietin is also protective (Abdelrahman et al. 2004; Cuzzocrea et al. 2006), as is the iron-binder lactoferrin (Tian et al. 2010) and as are anti-inflammatory statins (Durant et al. 2004; Gao et al. 2008; Kopterides and Falagas 2009). All of these observations make it very clear indeed that iron is intimately involved in the death following SIRS and sepsis, and—while not even mentioned in the guidelines (Dellinger et al. 2008)—that its effective chelation should be considered for research leading towards its inclusion as an important part of any therapy.

Bactericidal antibiotics

The classical test for if a bacterium is (or was) 'alive' is to analyze its ability to multiply, i.e. viability = culturability (Kell et al. 1998; Postgate 1967, 1976). Accordingly, bacterial antibiotics have long been classified into those that are bacteriostatic, i.e. stop individual cells growing but allow culturability to recover if the antibiotic is removed, and those that are bactericidal, i.e. that actually kill cells and thereby decrease the numbers of those that *are* culturable (capable of multiplication) even if the antibiotic is removed. Since this clearly implies that causing growth to cease is not of itself bactericidal, and anyway different antibiotics have a variety of different modes of action, it has always been a slight mystery as to what it is that makes a particular antibiotic bactericidal rather than merely bacteriostatic.

A very important paper (Kohanski et al. 2007) provides much of the answer. As one may suppose from the subject matter of this review, iron is again involved, specifically via the Fenton reaction in which poorly liganded ferrous ions reduce the comparatively harmless hydrogen peroxide to the deadly hydroxyl radical.

Based on a previous paper from the same group (Dwyer et al. 2007), Kohanski et al. (2007) (see also Davies et al. 2009; Dwyer et al. 2007, 2009; Imlay 2008; Kohanski et al. 2008; Liu et al.2009a; Wang and Zhao, 2009) reported that the three major classes of bactericidal antibiotics (exemplified by norfloxacin, ampicillin and kanamycin), regardless of drug–target interaction, utilize internal iron liberated from iron–sulphur clusters to promote Fenton-mediated hydroxyl radical formation in bacteria, that such hydroxyl radical generation contributes to the killing efficiency of these lethal drugs (probably via their known ability to damage DNA), and that in contrast antibiotics that are merely bacteriostatic do not cause the production of such hydroxyl radicals. The availability of multiple genetically marked strains allowed several predictions (such as the resistance to be expected in mutants that could not make iron-sulphur centres so effectively) to be tested successfully. Nitric oxide is correspondingly protective (Gusarov et al. 2009). This suggests, much as above, that there is a common mechanism of iron/hydroxyl-mediated cellular death underlying the action of all classes of bactericidal antibiotics and opens up many new possibilities for combination therapies based on promoting this kind of activity selectively (see Fig. 9). This said, how synergistic a combination is does depend on the exact speciation of the liganded iron; surprisingly, the iron chelator deferasirox *promoted* the antibacterial activity of ciprofloxacin against *V. vulnificus* (Neupane and Kim 2010), as did deferiprone with various azoles against *Aspergillus fumigatus*, while deferoxamine was antagonistic to azoles (Zarember et al. 2009). As with any complex system, the interactions can be highly dosedependent (Hegreness et al. 2008; Kohanski et al. 2010; Yeh et al. 2009).

Viruses

A typical viral infection involves the biding of virus to the cell surface followed by internalisation and other effects. Some viruses are especially virulent, and as well as inflammation cause the death of cells that they have invaded. It is obviously of interest to establish whether iron is involved in this kind of cell death (and if so whether iron chelation might contribute to a suitable therapy during the acute phase of an infection).

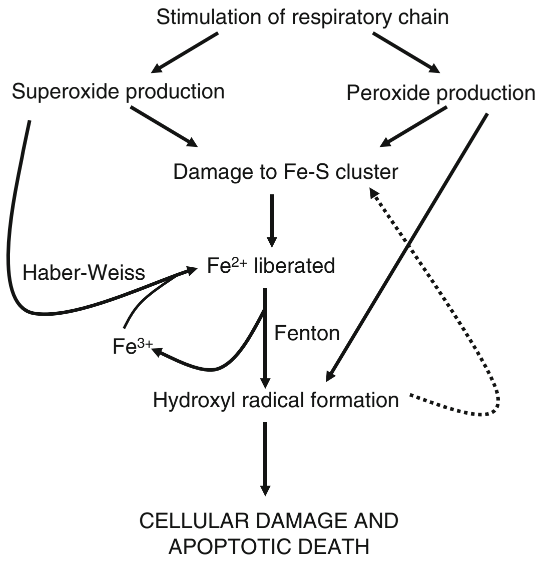


Fig. 9 A diagram, based very loosely on the narrative in (Kohanski et al. 2007), illustrating how the autocatalytic activity of the reactions of superoxide, peroxide and the hydroxyl radical involving poorly liganded iron can exert a positive feedback leading to the death of cells

The above suggestions are certainly true of infections caused by **influenza A** (Visseren et al. 2002) (see also Akaike et al. 1996; Beck et al. 2004), **herpes simplex virus** (Gennero et al. 2010; Lamey and Biagioni 1995; Romeo et al. 2001), **hepatitis C** (Alavian and Tabatabaei 2009; Alla and Bonkovsky 2005; Ameli et al. 2008; Bassett 2007; Batts 2007; Bonkovsky 2002; Bonkovsky et al. 2006; Desai et al. 2008; Di Marco et al. 2008; Drakesmith and Prentice 2008; Fargion et al. 2002; Ferrara et al. 2009; Franchini et al. 2008; Fujita et al. 2007a, b; Fujita and Takei 2007; Girelli et al. 2009; Gürkan et al. 2005; Guyader et al. 2007; Hayashi and Yano 2002; Heathcote 2004; Kaito 2007; Kaito et al. 2006; Kato et al. 2001, 2007; Ko et al. 2007; Mahmoud et al. 2008; Mueller et al. 2006; Nahon et al. 2008; Nishina et al. 2008; Otogawa et al. 2008; Price and Kowdley 2009; Rigamonti et al. 2005; Sebastiani and Walker 2007; Sikorska et al. 2010; Sugimoto et al. 2009; Tanaka et al. 2007; Tanaka and Kiyosawa 2004; Trinder et al. 2008; Tung et al. 2003; Valenti et al. 2008; Venturini et al. 2010; Won et al. 2009) and **HIV** (Boelaert et al. 1996; Butensky James et al. 2009; de Monyé et al. 1999; Debebe et al. 2007; Drakesmith and Prentice 2008; Georgiou et al. 2000; Gordeuk et al. 2001, 2006; Kagu et al. 2007; Ketonen et al. 1996; McDermid et al. 2007; McDermid and Prentice 2006; McDermid et al.

2009; Meyer 2006; Northrop-Clewes 2008; Rawat et al. 2008; Savarino et al. 1999; Schreck et al. 1992; Szajerka and Jablecki 2007; Traoré and Meyer 2004, 2007; van Asbeck et al. 2001; Weinberg 2006; Ziegler et al. 2001).

Microbial, plant and animal toxins

Before considering chemical toxicants, it is worth noting that the natural world contains a very great many molecules that are toxic to cells and hence organisms. Although the mechanisms of cell death are rather rarely pursued, there is evidence for the involvement of iron in the sequelae of exposure to toxic doses of gentamicin (Petronilho et al. 2009), ochratoxin (Hasinoff et al. 1990; Omar et al. 1990; Størmer and Hoiby 1996) and ricin (Hassoun and Wang 1999; Kumar et al. 2003; Muldoon et al. 1996), as well as to certain snake venoms (Gutierrez et al. 2010).

Chemical toxicants: aniline, asbestos, dioxins, hydrazines, methyl mercury and paraquat

The most dangerous kinds of man-made toxic chemical agents, those that kill cells or organisms, exhibit a rich diversity of chemical structures and can bind to multiple cellular targets, to the extent that a unitary mode of action is not considered likely. (This said, the same was thought to be true for the mode of action of general anaesthetics or narcotics, and they turn out to have a comparatively small number of rather specific protein targets (Dobson et al. 2009; Dobson and Kell 2008; Franks 2006, 2008; Grasshoff et al. 2006)). However, this does not mean that multiple initial events do not at some point converge to a comparatively small number of crucial events of cell death (whether through necrosis or apoptosis, Vanden Berghe et al. 2009), equivalent to the 'bow-tie' model of cellular networks (see e.g. Csete and Doyle 2004; Ma'ayan 2009; Ma et al. 2004, 2007; Ma and Zeng 2003; Oda and Kitano 2006; Rodríguez-Caso et al. 2009; Wang and Chen 2010; Zhao et al. 2006, 2010) and (Fig. 10), and my purpose here is to highlight the evidence that iron-based mechanisms, largely based on Fenton chemistry, are involved in a number of these cases. A recent special issue on toxicants and neurodegeneration is also of interest here (Gupta and Milatovic 2009).

Acetaminophen

Acetaminophen (paracetamol in the United Kingdom) (ChEBI 46195) is a well-known analgesic that is nevertheless highly toxic at concentrations in excess of the therapeutic dose, as it is converted to the electrophilic N-acetyl-p-benzoquinone imine (NAPQI). If glutathione is in insufficient supply, the NAPQI cannot be conjugated harmlessly by glutathione and so it reacts covalently with proteins, especially mitochondrial proteins (Hinson et al. 2004; Jaeschke and Bajt 2006; Kon et al. 2004; Masubuchi et al. 2005; Reid et al. 2005), resulting in apoptotic cell death and organismal death via liver damage (e.g. Barker et al. 1977; Beckett et al. 1989; James et al. 2003; Martin-Murphy et al. 2010; Olaleye and Rocha 2008). One of the effects of mitochondrial damage is iron release, and it has long been known that iron chelators help prevent this toxicity (Sakaida et al. 1995; Schnellmann et al. 1999). Appropriate hydroxyl radical scavengers are also partly protective (Chandrasekaran et al. 2009), while lactoferrin is also protective, although not apparently only via its iron-binding capacity (Yin et al. 2010).

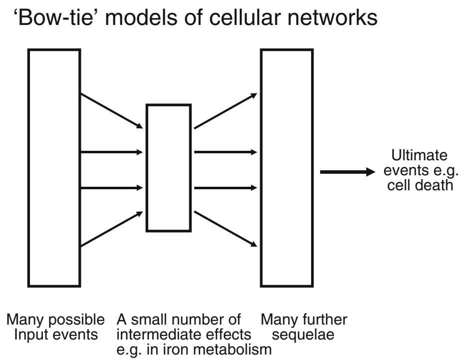


Fig. 10 'Bow-tie' models of cellular networks. There are many examples of cellular networks in which a large variety of possible initial events leads to complex sequelae, but these are mediated via a comparatively small number of 'intermediate' reactions. While in the present case it is suggested that these in part involve complex positive feedbacks, the general 'bow-tie' idea does allow one to recognise that despite the many different possible inputs, a broadly unitary kind of mechanism of action—here involving iron dysregulation—can reasonably be invoked to explain the multiple causes that can lead to cell death and destruction

Aniline

As is well known, the adulteration with aniline of cooking oil in Spain showed that aniline so administered can be exceedingly toxic to humans (the 'toxic oil syndrome', Hill et al. 1987; Vázquez Roncero et al. 1983), especially in the lungs and spleen. It is now clear (Bomhard and Herbold 2005; Khan et al. 1995, 1999; Ma et al. 2008; Mellert et al. 2004; Wang et al. 2005, 2008, 2010) that iron is heavily involved in this via Fenton chemistry.

Asbestos

Many mutagens are carcinogens, typically by intercalating into DNA, so it was not a priori obvious why asbestos fibres—enormously larger than the diameter of DNA—should be so toxic. The mystery was solved when it was realised that asbestos does in fact contain and bind iron, that the sharp surface of the iron-loaded fibres can catalyse hydroxyl radical formation and that it is *this* that provides the toxic mechanism (Aljandali et al. 2001; Burrows and Muller 1998; Chao et al. 1996; Chen et al. 1996; Dai and Churg 2001; Fubini and Arean 1999; Gilmour et al. 1997; Governa et al. 1999; Gulumian and van Wyk 1987; Hardy and Aust 1995a, b; Hippeli and Elstner 1999; Jaurand 1997; Kamp et al. 1992; Kamp and Weitzman 1997, 1999; Kelleher et al. 2000; Levresse et al. 2000; Lund and Aust 1991, 1992; Mossman and Churg 1998; Mossman et al. 1987; Park and Aust 1998; Quinlan et al. 1994; Shatos et al. 1987; Shen et al. 1995; Weinberg 1989; Weitzman and Graceffa 1984; Xu et al. 1999; Azad et al. 2008; Bhattacharya et al. 2005; Daghino et al. 2006; Fantauzzi et al. 2010; Fattman et al. 2006; Gazzano et al. 2007; Ghio et al. 2004, 2009; Heintz et al. 2010; Kamp 2009; Knaapen et al. 2004; Liu et al. 2010; Nymark et al. 2008; Panduri et al. 2006; Poser et al. 2004; Quinlan et al. 2002; Shannahan et al.; Shukla et al. 2003a, b; Sørensen et al. 2007; Toyokuni 2009a, b; Upadhyay and Kamp 2003; Valavanidis et al. 2009).

Dioxins

Dioxins are formed typically via the thermal combustion of halogen-containing compounds, and a chief product, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, often referred to simply as 'dioxin' (ChEBI 28119), notoriously produced during the 1976 Seveso chemical plant explosion and as an impurity in Agent Orange (a roughly 1:1 mixture of the plant hormone (auxin—ChEBI 22676) analogues) 2,4-dichlorophenoxyacetic acid (2,4-D; ChEBI 28854) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T; ChEBI 27903), is both a cause of chloracne and is a hepato-carcinogen. It was found that mice low in iron are resistant to this hepatotoxicity however (Poland and Knutson 1982; Sweeny et al. 1979), strongly implicating iron. In addition, iron enhances the toxicity of dioxin (Al-Turk et al. 1988; Smith et al. 1998) while iron chelators reduce it (Al-Bayati and Stohs 1987; Wahba et al. 1990). While the exact details have still not been worked out, there is little doubt that iron is important in the toxicity of a wide variety of polyhalogenated aromatics (Smith and Chernova 2009; Smith and Elder 2010), including hexachlorobenzene (ChEBI 5692) (Franklin et al. 2005).

Hydrazines

Phenylhydrazine (ChEBI 27924) (like other hydrazines) is a reactive substance that is commonly used in toxicity studies. It is known (Agrawal et al. 2001; Atanasova et al. 2004; Ferrali et al. 1997a, b; Fraenkel et al. 2009; Karbownik et al. 2000; Kim et al. 2009; Latunde-Dada et al. 2004; Rokushima et al.2007a, b; Sharma and Haldar 2009; Yamamoto and Kawanishi 1992) to induce haemolytic anaemia and iron release and thence cytotoxicity. Melatonin can be protective (Sharma and Haldar 2009).

Methyl mercury

Originally highlighted via 'Minamata disease' (a prominent symptom of which, as with many neurological disease, is ataxia), methylmercury (ChEBI 30785) is a well-known neurotoxicant (Clarkson et al. 2003). Like most if not all other xenobiotics (Dobson et al. 2009a; Dobson and Kell 2008; Dobson et al. 2009b; Kell and Dobson 2009), it requires one or more carriers for cellular uptake—in this case, when complexed to L-cysteine, the 'large amino acid' transporter (Kanai and Endou 2003; Simmons-Willis et al. 2002; Yin et al. 2008). There is certainly evidence that exposure to this agent causes oxidative stress (Ali et al. 1992; Aschner et al. 2007; Atchison and Hare 1994; Franco et al. 2009; Johansson et al. 2007; Sanfeliu et al. 2003; Sarafian et al. 1994; Yee and Choi 1994, 1996; Yin et al. 2007) and raises cellular iron levels (Ilbäck et al. 2000) and that anti-oxidants (Daré et al. 2000; Kaur et al. 2006; Sarafian and Verity 1991; Shanker and Aschner 2003; Usuki et al. 2001; Watanabe et al. 2009; Yamashita et al. 2004; Zurich and Monnet-Tschudi 2009), metallothioneins (West et al. 2008) and/or iron chelators (Castoldi et al. 2001; LeBel et al. 1992; Sarafian and Verity 1991; Stohs and Bagchi 1995) can be protective. Taken together, this does imply strongly a role for iron-mediated cytotoxicity of the type highlighted herein in the pathogenesis of methylmercury poisoning.

Paraquat

Paraquat (N,N′-dimethyl-4,4′-bipyridinium dichloride; ChEBI 34905) is a well-known herbicide and toxicant, whose mode of action relies on the generation of superoxide radicals. As such, its toxicity may be expected to be exacerbated by iron, and this is the case (Andersen 2003; Ayaki et al. 2005; Fernandez et al. 2000; Peng et al. 2007, 2009). In addition, again as expected from the above (and consistent with its structural similarity to the Parkinson-inducing agent MPTP-1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, ChEBI 17963), it can induce Parkinson-like symptoms (Kaur et al. 2009; Miller et al. 2009; Ossowska et al. 2006; Peng et al. 2007, 2009). The protection by molecules—such as ferritin (Kaur et al. 2009) and polyphenols (Jimenez-Del-Rio et al. 2010)—capable of chelating iron harmlessly is thus of considerable interest.

Other toxicants in which iron release has been implicated as part of the mechanisms of their toxicity

The list of known and potential toxicants is limitless, and part of the role of this review is to alert domain experts to the likelihood that iron, and dysregulation in iron metabolism, may mediate the toxicity of such molecules (and thus that its chelation may be important, under both acute and chronic conditions, in assisting resolution of the toxicity). To this end, I note the role of iron-induced oxidative stress in the toxicity of anthracyclines (including adriamycin/doxorubicin ChEBI 28748) (Ceyssens et al. 2004; Kaiserová et al. 2007; Kotamraju et al. 2002, 2004; Luft 2006; Othman et al. 2008; Šimůnek et al. 2009; Thougaard et al. 2010; Xu et al. 2008), arsenic (De Vizcaya-Ruiz et al. 2009; Fujihara et al. 2009), beer brewed in cast iron pots (Kew and Asare 2007), bleomycin (ChEBI 3139) (Wu et al. 2004; Yang et al. 2010), C60 fullerenes (Usenko et al. 2008), carbon nanotubes (Murray et al. 2009) (and see Guo et al. 2007; Jurkschat et al. 2007), carbon tetrachloride (Mansour 2000; Ogeturk et al. 2004), organophosphates (Goel et al. 2006), sulphur mustard agents (Korkmaz et al. 2008; Korkmaz et al. 2006; Naghii 2002) and talc nanoparticles (Akhtar et al. 2010). Welding fumes are toxic and contain both iron and manganese (Flynn and Susi 2010; Sriram et al. 2010), and the toxicity of nano-iron itself has also been studied (Li et al. 2009).

Apoptosis or necrosis?

As is well known, cells can die by both necrosis and by a more regulated form, apoptosis. While this—nor ‘normal’ ageing (summarised e.g. by Bishop et al. 2010b; Finkel 2005; Franco et al. 2007; Gems 2009; Kenyon 2010; Kirkwood 2008; Muller et al. 2007; Vaupel 2010), in which various degradative processes including iron dysregulation can be implicated (e.g. Brewer 2010; Cass et al. 2007; Cook and Yu 1998; Facchini 2002; Galaris et al. 2008; Kell 2009a; Kujoth et al. 2005; Kurz et al. 2008b; Massie et al. 1983; Napoli et al. 2006; Pfefferbaum et al. 2009; Terman et al. 2010; Xu et al. 2010)—is not the focus of this review, it is reasonable to enquire as to what kind of evidence exists for the mechanism(s) of cell death contingent upon iron dysregulation. As it turns out, while there is a little evidence that iron overload can cause necrosis (Babatasi et al. 1996; Traoré and Meyer 2007; Vanden Berghe et al. 2009; Vanlangenakker et al. 2008), there is abundant evidence for the ability of iron to cause apoptosis (Kotamraju et al. 2004a, b; Kurz et al. 2007, 2008b; Vanden Berghe et al. 2009), and—depending presumably on the exact liganding of the iron (Kell 2009a)—this can be effected when iron is ostensibly depleted (e.g. Bergman et al. 2005; Bidle and Bender 2008; Brard et al. 2006; Buss et al. 2003; Fukuchi et al. 1994; Greene et al. 2002; Haq et al. 1995; Hileti et al. 1995; Jiang et al. 2002; Jin et al. 2007; Koc et al. 2006; Kovář et al. 1997, 2001; Leardi et al. 1998; Lee et al. 2006b, c; Pan et al. 2004; Simonart et al. 2000; Sun et al. 2009; Truksa et al. 2003; Zhang et al. 2003; Zhao et al. 2004) or in excess (e.g. Aljandali et al. 2001; Cozzi et al. 2003, 2010; Devireddy et al. 2005; Franke et al. 2010; Jacob et al. 1997, 2000; Javadi et al. 2004; Jímenez Del Río and Vélez-Pardo 2004; Kamp et al. 2002; Kawabata et al. 1997; Kermer et al. 2004; Kooncumchoo et al. 2006; Kruman et al. 1997; Kummer et al. 2008; Kurz et al. 2007, 2008b; Lakshmi Devi and Anuradha 2009; Lee et al. 2006d; Levenson 2005; Lu et al. 2008; Ma et al. 2009; Messer et al. 2009; Murakami et al. 2006; Natoli et al. 2009; Persson 2005; Polla et al. 2003; Schlawe et al. 2004; Shin and Kim 2009; Shukla et al. 2003; Tenopoulou et al. 2005; Upadhyay and Kamp 2003; Vélez-Pardo et al. 1997; Zhao et al. 1997).

Inflammation and NF-κB

As reviewed in the previous survey (Kell 2009a) and elsewhere (e.g. Shoelson and Goldfine 2009; Shoelson et al. 2007), inflammation lies at the heart of many of these processes, and pathways involving NF-κB (see e.g. http://www.nf-kb.org/) are especially core here (e.g. Ali and Mann 2004; Circu and Aw 2010; Granic et al. 2009; Karin 2008; Karin and Greten 2005; Li et al. 2005; Maeda and Omata 2008; Simmonds and Foxwell 2008; Zhang and Rigas 2006). Of particular relevance in ROS/iron metabolism are the facts that **NF-κB is redox-sensitive** (e.g. Aggarwal and Sung 2009; Baeuerle and Henkel 1994; Chandrasekaran and Taylor 2008; Cho et al. 1998; Dröge 2002; Fulda et al. 2010; Galaris et al. 2008; Gloire et al. 2006; Gloire and Piette 2009; Ha et al. 2010; Haddad et al. 2000; Hayashi et al. 1993; Janssen-Heininger et al. 2008; Lagan et al. 2008; Lukosz et al. 2010; Nishi et al. 2002; Phillips et al. 2010; Schreck et al. 1991, 1992; Schreck and Baeuerle 1994; Sen and Packer 1996; She et al. 2002; Surh et al. 2005; Surh and Na 2008; Thannickal and Fanburg 2000; Trachootham et al. 2008, 2009; Valko et al. 2007; Weinberg and Chandel 2009; Wondrak 2009; Xiong et al. 2003) and that there are links between NF-κB and NGAL/lcn2 (Bu et al. 2006; Cowland et al. 2003, 2006, 2008; Karlsen et al. 2010) and/or hepcidin (Sow et al. 2009; Tacchini et al. 2008). Specificity is likely to come, in part, via the frequency encoding of NF-κB activity (Ashall et al. 2009; Nelson et al. 2004).

Catalytic behaviour of polypeptides and proteins

I have mentioned several times the idea that different proteins can bind unliganded iron to catalyse the production of hydroxyl radical, and it is certainly the case that the degree of liganding can affect these kinds of activities (Kell 2009a). Here it is appropriate to highlight the abilities of polypeptides and even poly(aminoacids)—whether binding metals (or not)—to exhibit catalytic activities, e.g. poly(leucine) (Carrea et al. 2005; Porter et al. 1999), and how adding metals to polypeptides to make metalloenzymes can have huge effects on their catalytic activities (Pierron et al. 2008; Pordea and Ward 2008; Turner 2009). The recent development of orthogonal ribosomes capable of incorporating novel amino acids into polypeptides (Neumann et al. 2010) opens up considerable possibilities here.

Dietary and/or pharmacological treatment of iron-mediated toxicity

Pharmaceutical

Developing novel pharmaceutical agents is a costly enterprise, and many candidate drugs fall by the wayside during the development process (see e.g. Dobson et al. 2009b; Kola and Landis 2004; Leeson and Springthorpe 2007). As most recently reviewed (Agarwal 2010; Berdoukas et al. 2009; Bolognin et al. 2009a; Cappellini and Pattoneri 2009; Cappellini et al. 2010; Clifton et al. 2009; Hider et al. 2008; Kell 2009a; Kontoghiorghes et al. 2010; Kwiatkowski 2010; Mladěnka et al. 2009; Pennell et al. 2010; Perez and Franz 2010; Richardson et al. 2009b and references therein), a number of (pharmacological drug) approved iron chelators do exist and thus clearly have the potential to prove beneficial in treating diseases and the sequelae of toxin exposure whose aetiology involves poorly liganded iron via the Fenton reaction. The benefits of administration of desferrioxamine in Alzheimer's, for instance, have been known for nearly 20 years (Crapper McLachlan et al. 1991), benefits since observed with other iron chelators (e.g. Amit et al. 2008; Bolognin et al. 2009a; Bush 2008; Liu et al. 2009b, 2010b; Perez and Franz 2010; Smith et al. 2010; Zhang et al. 2009). The implications for this and other neurodegenerative diseases—and potentially for the more acute and even chronic effects of other toxins—are obvious. Those approved clinically include Deferoxamine (Desferal; ChEBI 31460), Deferiprone (Ferriprox; PubChem CID 2972) and Deferasirox (Exjade; ChEBI 49005) (Fig. 11). Note that—unlike the other two—Deferoxamine is not orally active and must be injected, and even then may fail to cross cellular membranes to exert its action appropriately (Warkentin et al. 2010).

Dietary or nutritional/nutraceutical

In addition, many organisms make so-called 'secondary' or *natural products*, whose functions are often unclear but

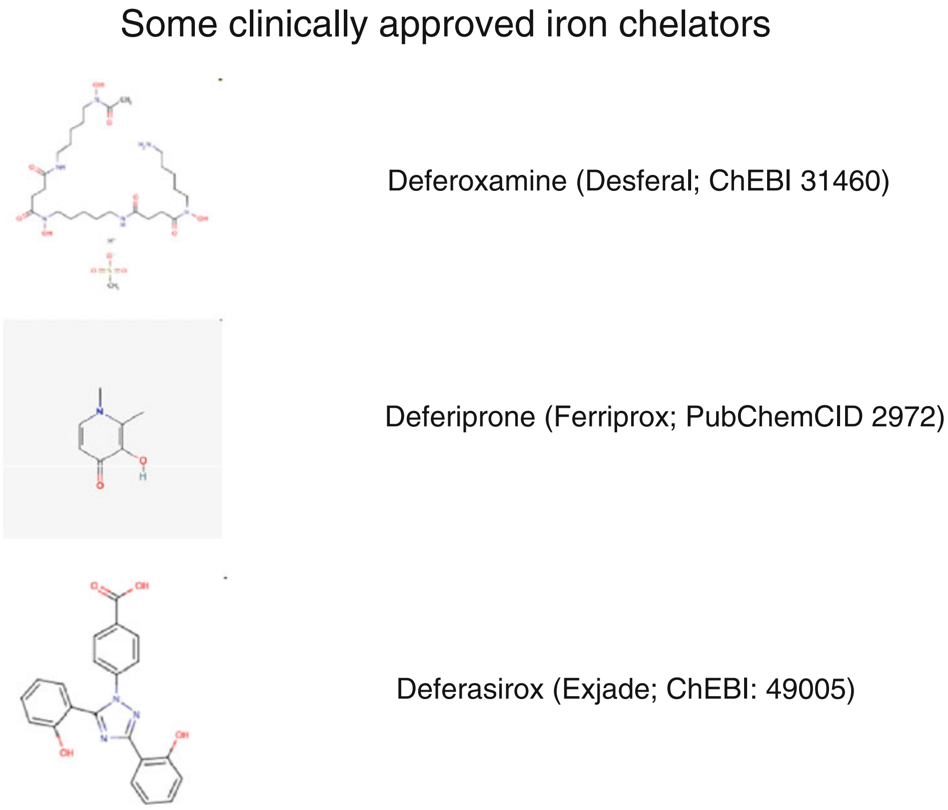


Fig. 11 The three main iron chelators approved for clinical use

that clearly have evolutionary benefits for the host (Hadacek et al. 2010; Kell et al. 1995). As I also reviewed (Kell 2009a), many **iron-chelating** natural products exist in (or may be added to, Pócsi et al. 2008) foodstuffs for which no full pharmaceutical regulatory controls are required and which are classed as nutritional substances. Many are **polyphenols** (ChEBI 26195) (Amic et al. 2007; Arts and Hollman 2005; Auclair et al. 2009; Cemeli et al. 2009; Cheynier 2005; Geronikaki and Gavalas 2006; Halliwell 2007; Jovanovic and Simic 2000; Kandaswami and Middleton 1994; Kiokias et al. 2008; Korkina and Afanas'ev 1997; Linseisen and Rohrmann 2008; Loke et al. 2009; Manach et al. 2004, 2005a, b; Pérez-Jiménez et al. 2010; Perron and Brumaghim 2009; Perron et al. 2008; Petti and Scully 2009; Pietta 2000; Rice-Evans and Packer 2003; Scalbert et al. 2005; Scalbert and Williamson 2000; Seifried et al. 2007; Slemmer et al. 2008; Spencer et al. 2008; Yadav and Bhatnagar 2007a, b, 2010), including the anthocyanins that proved chemoprotective (Butelli et al. 2008) in a mouse p53 cancer model. Since the previous review (Kell 2009a), I would draw particular attention to a comprehensive overview of the subject (Perron and Brumaghim 2009), as well as new reviews and papers on the chief polyphenol in green tea, (−)**epigallocatechin-3-gallate** (ChEBI 4806) (Adhami et al. 2009; Butt and Sultan 2009; Hsieh et al. 2009; Jimenez-Del-Rio et al. 2010; Johnson et al. 2010; Pandey and Gupta 2009; Paterniti et al. 2009; Ramesh et al. 2009; Reznichenko et al. 2010; Suh et al. 2009; Weinreb et al. 2009a), on **curcumin** (ChEBI 3962) (a constituent of turmeric) (Aggarwal and Harikumar 2009; Aggarwal and Sung 2009; Anand et al. 2010; Basile et al. 2009; Epstein et al. 2009; Hegde et al. 2009; Iqbal et al. 2009; Jiao et al. 2009; Jurenka 2009; Kalpravidh et al. 2010; Majumdar et al. 2009; Messner et al. 2009; Patil et al. 2009; Ravindran et al. 2009; Rivera-Espinoza and Muriel 2009; Thephinlap et al. 2009; Thomas et al. 2009; Tuntipopipat et al. 2009; Wang et al. 2009a), on **eugenol** (ChEBI 4917) (Nagababu et al. 2010) (and cf. Allen and Cornforth 2009), on nepetoidin caffeic acid esters (Maioli et al. 2010), on **quercetin** (ChEBI 16243) (Chobot 2010; Kitagawa et al. 2009; Krukoski et al. 2009; Lorrain et al. 2010; Park et al. 2010; Pavlica and Gebhardt 2010; Smirnova et al. 2009; Terao 2009; Vlachodimitropoulou et al. 2010) and on **melatonin** (CHEBI 16796) (Borah and Mohanakumar 2009; Korkmaz et al. 2008, 2009; Reiter et al. 2009; Sener et al. 2009; Sharma and Haldar 2009; Signorini et al. 2009). Many of the protective effects observed are likely due to the iron chelating, as well as directly antioxidative (redox) properties of these molecules (e.g. Ferrali et al. 1997a; Hague et al. 2006; Halliwell 2009; Halliwell et al. 2005; Hider et al. 2001; Končić et al. 2010; Lopes et al. 1999; Mandel et al. 2004; Mandel and Youdim 2004; Morel et al. 1994; Nijveldt et al. 2001; Rice-Evans et al. 1997; Rice-Evans and Packer 2003; Weinreb et al. 2007, 2009a; Yoshino and Murakami 1998). Other molecules that are not themselves directly antioxidant, but have iron-binding characteristics, may also be of benefit. This is certainly true of **phytic acid** (phytate; myo-inositol-1,2,3,4,5,6-hexakis phosphate; CHEBI 17401) (Aljandali et al. 2001; Allen and Cornforth 2009; Brune et al. 1989; Davidsson et al. 1994; Doria et al. 2009; Glahn et al. 2002; Graf and Eaton 1990, 1993; Graf et al. 1987; Grases et al. 2001; Hallberg et al. 1989; Han et al. 1994; Hanson et al. 2006; Hawkins et al. 1993; Kamp et al. 1995a, b, 2002; Kim et al. 2008; Kumar et al. 2010; Minihane and Rimbach 2002; Miyamoto et al. 2000; Panduri et al. 2006; Poser et al. 2004; Rao et al. 1991; Rimbach et al. 2008; Sandberg et al. 1999; Schlemmer et al. 2009; Shamsuddin 1995; Vucenik and Shamsuddin 2006; Xu et al. 2008).

Phlebotomy

In addition, as follows implicitly from Sullivan's 'iron hypothesis' (Sullivan 1981, 2001, 2003, 2004) (and see Kell 2009a), one way to decrease the amount of iron in the body is to remove it by blood-letting or phlebotomy. While phlebotomy is a very traditional nostrum, often assumed or considered to have rather dubious or at best modest scientific support, there is in fact increasing literature implying its benefits in a variety of conditions (e.g. Aigner et al. 2008; Beutler 2007; Broedbaek et al. 2009; Brudevold et al. 2008; Busca et al. 2010; DePalma et al. 2007, 2010; Dereure et al. 2008; Desai et al. 2008; Dwyer et al. 2009; Equitani et al. 2008; Facchini et al. 2002; Fargion et al. 2002; Fernández-Real et al. 2002; Fujita et al. 2009; Fujita and Takei 2007; Hayashi et al. 2006; Hayashi and Yano 2002; Heathcote 2004; Horwitz and Rosenthal 1999; Hua et al. 2001; Kaito 2007; Kaito et al. 2006; Kato et al. 2001, 2007; Kom et al. 2006; Rajpathak et al. 2009; Sullivan 2009; Sumida et al. 2009; Tanaka et al. 2007, 2009; Toyokuni 2009b; Zacharski et al. 2008). Plausibly such benefits are due to its role in decreasing iron stores.

Discussion: toxicology as systems biology

> "When sorrows come, they come not single spies but in battalions." (Shakespeare, Hamlet.)

It is certainly the case that reasons for the co-occurrence of two or more observables are that one causes the other or they have the same, separate cause. Since I have argued strongly here for the essentiality of iron dysregulation in a variety of syndromes (and have omitted many others, such as non-alcoholic (Baptista-Gonzalez et al. 2008; Kirsch et al. 2006; Kowdley 2010) or alcoholic liver disease (Breitkopf et al. 2009; Lecube et al. 2009)), and indeed cancers of various kinds (see Kell 2009a), the implication is that iron dysregulation can manifest in multiple different ways and that these might co-occur. There is considerable and increasing evidence for that (see e.g. Adibhatla and Hatcher 2010; Baker et al. 2009; Beeri et al. 2008; Cole et al. 2007; Franco et al. 2009; Janson et al. 2004; Kell 2009a; Li and Hölscher 2007; Mascitelli et al. 2009; Neumann et al. 2008; Pandolfo 2009; Roriz-Filho et al. 2009; Schnaider Beeri et al. 2004; Starley et al. 2010; Utzschneider and Kowdley 2010; Verduzco and Nathan 2009; Xu et al. 2009), with the exact outcomes being determined by different levels of expression (see for instance http://www.proteinatlas.org/) of different proteins in different tissues.

In a similar vein, it is not news (Attwood et al. 2009; Evans 2008; Hull et al. 2008; Kostoff 2002) that the large floods of literature have led to something of a 'balkanisation' of the literature into increasingly specialised segments, and that this makes it hard to seek to bring together such disparate parts of the literature so as to draw out general truths (Dobson and Kell 2008; Kell 2009a), via the methods of inductive reasoning (Kell and Oliver 2004; King et al. 2004, 2009). As previously discussed, it is well established on theoretical grounds alone that the activity of any step in a biochemical network can influence the concentration of any variable (such as—fleetingly—the amount of hydroxyl radicals produced). Thus, while it is better to derive quantitative models (e.g. Coveney and Fowler 2005; Csikasz-Nágy 2009; Kell 2006a, b; Kell and Knowles 2006; Kell and Westerhoff 1986a, b; Milo et al. 2010; Mogilner et al. 2006; Noble 2002, 2006, 2010; Oates et al. 2009; Phillips and Milo 2009; Tomlin and Axelrod 2007), at the very minimum one should be looking qualitatively at those factors that should be increased or decreased in order to improve the organism's ability to resist oxidative stress (Fig. 12).

Indeed, it is the very act of doing this that leads one to recognise these kinds of complex problems as problems of systems or network biology (Alon 2006; Klipp et al. 2005; Palsson 2006). What do I mean by this?

A systems biology view of toxicology: toxicology as systems biology

In the present case, I have adduced evidence that a range of distinct aetologies, which manifest as a variety of different syndromes or diseases, converge at some point on an autocatalytic series of reactions, involving imperfectly liganded iron, in the production of the very damaging hydroxyl radical, that by causing the destruction of appropriate cellular structures and proteins liberates further 'free' iron and other reactive oxygen species, thereby effecting positive feedback (also known as 'vicious cycles', Lin and Beal 2006; Proctor and Gray 2010; Proctor et al. 2007) that leads to the production of yet further damage. The implication of this is that to be more specific we need suitable network models of the biological systems of interest (Kell 2007), and of how toxicants of any kind can interact with their components.

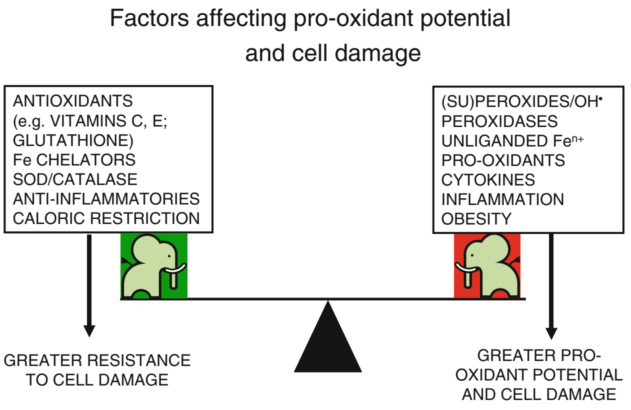


Fig. 12 The extent of cell damage caused by the unliganded iron-catalysed production of ROSs and RNSs is determined by many factors, some of which promote and some of which act against it. While the existence of hormesis (see text) means that the see-saw illustrated here is an imperfect metaphor, the diagram serves to illustrate the complexity of the problem and the need for a systems biology approach to its solution

Of course in the steady state, the amount of a substance is governed both by the processes that create it and those that decompose it (Fig. 13), and individual effects of particular substances can vary qualitatively depending on concentrations, as in hormesis (e.g. Calabrese 2008a, b, c; Calabrese and Baldwin 1997, 2001, 2003; Calabrese and Blain 2005, 2009; Cook and Calabrese 2006; Cox 2009; Gems and Partridge 2008; Gómez-Pinilla 2008; Hadacek et al. 2010; Hayes 2009; Hoffmann 2009; Mattson 2008a, b; Radak et al. 2008; Rattan 2004, 2008; Rattan and Demirovic 2009;

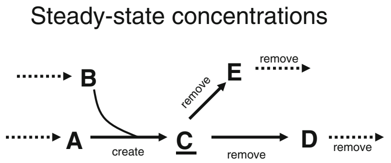


Fig. 13 The steady-state concentrations of a molecule depend on the rates of production and removal of the molecule in question. Both lowering creation and increasing removal represents a particularly effective strategy relative to doing just one of these alone. Thus if C is the hydroxyl radical we can lower its concentration by decreasing A and/or B and by increasing the rates of the reaction to D and E. The latter (decrease of concentration of C) may sometimes better be effected by increasing the activities of enzymes yet further downstream

Ristow and Zarse 2010; Sørensen et al. 2009), so any analysis should be a systems analysis. The simple fact that, for instance, iron chelators improve prospects in Alzheimer's implies that there is a background level of *natural* repair (otherwise chelators would only slow the neurodegeneration and not reverse it) and that is not necessarily apparent from measuring only net effects. Hence, the need for accurate systems biology models.

The very fact that multiple reactions typically lead to the creation (and destruction) of a given metabolite (such as the hydroxyl radical) means that to minimise its concentration it is best to modify many reactions simultaneously. This exceptionally important point from systems biology should underpin any scientific and therapeutic programs.

Systems biology methods

Systems biology methods are typically classified into 'forward' and inverse' (Fig. 14). For the purposes of this discussion, I shall concentrate on *metabolic* networks (in contrast to signalling networks they transfer both matter and information, Kell 2004). Metabolic and other networks are 'graphs' in that they consist of entities ('nodes', such as metabolites) that interact with each other via 'edges' (enzymatic reactions). There may of course be other interactions such those that do not involve substrates or products but are mediated via molecules (effectors) that modify the rates of reactions. The distinction between forward and inverse models is based on whether one starts with the parameters or variables of the system. In metabolic networks, the parameters are typically the starting concentrations of substances present and the kinetic constants (K_m, K_i, V_{max}, etc.) of the enzymes. The variables are typically the concentrations of metabolic intermediates, and the metabolic fluxes that change over time until a steady state (if such exists) is attained. It is important to note that only the parameters control the system. In *forward systems biology*, we thus seek to create a model of the network based on its parameters, and this is done in four phases, the first two of which are qualitative and the second quantitative (Herrgård et al. 2008; Kell and Knowles 2006; Thiele and Palsson 2010).

Forward and inverse methods
in systems biology

Forward: start with the system's parameters
(including its topology, kinetic constants and the
'starting' concentrations) and model the time
evolution of its variables

Inverse: start with the time series of the system
variables and seek to infer the topology and
parameters of the system that could produce them

Fig. 14 The relationship between 'forward' and 'inverse' methods of systems biology. The comparison of two 'inverse' systems (one a control and one treated with a toxin) in terms of the estimation of which parameters have changed most allows one to infer the sites or modes of action of that toxin [In a related manner we also discriminate forward and reverse genetics, including chemical genetics (Kell 2006a, b)].

Forward modelling

The first qualitative stage is one in which are listed all the reactions that are known to occur in the system or organism of interest; in the modern era, and especially for metabolic networks, these reaction lists are often derived in part from genomic annotations (Arakawa et al. 2006; Palsson 2006) with curation based on literature ('bibliomic') data (Duarte et al. 2007; Thiele and Palsson 2010). A second stage, again qualitative, adds known effectors (e.g. those involved in forming feedback loops), while the third and fourth stages—essentially amounting to molecular enzymology—include the known kinetic rate equations and the values of their parameters. Armed with such information, it is then possible to provide stochastic and ordinary differential equation models of the entire metabolic network of interest. In some cases, it is possible to make simplifying assumptions that require minimal knowledge of the kinetic parameters of the system and allow one to generate a time series of the system variables (Smallbone et al. 2007). An attractive feature of metabolism, for the purposes of modelling, is that, in contrast to signalling pathways, metabolism is subject to direct thermodynamic and (in particular) stoichiometric constraints (Palsson 2006). These constraints are extremely important in reducing the search space for the values of the kinetic parameters of the model, and indeed constrain significantly the states that the system *can* adopt (Kell 2004; Palsson 2006).

The modelling community has access to many tools, which are interoperable because they can be exchanged using community standards (Kell 2008) of which the most popular (Klipp et al. 2007) is SBML, the Systems Biology Markup Language (Hucka et al. 2003) (http://www.sbml.org/). Models are best made, and made available, in SBML. In addition, there is recognition that it is desirable to be clear about the *meaning* (semantics) of the elements in the model (Ananiadou et al. 2006; Attwood et al. 2009; Kell and Mendes 2008), since SBML puts no constraints on the names given to entities, and we have pioneered (Herrgård et al. 2008; Pettifer et al. 2009) the use of semantic annotation of all the entities, whether by reference to persistent databases or via database-independent means (e.g. the use of SMILES (Weininger 1988) and InChI (Coles et al. 2005; Stein et al. 2003) strings for small molecules). This is consistent with the MIRIAM proposals for describing the contents of a model accurately (Le Novère et al. 2005), and we have also used (Herrgård et al. 2008) the Systems Biology Ontology (http://www.ebi.ac.uk/sbo/)

and the Gene Ontology (http://www.geneontology.org/) as especially pertinent and useful ontologies. Tools also exist for creating such networks using CellDesigner (http://www.celldesigner.org/) and SBMLMerge (Schulz et al. 2006) for merging submodels, including visualising them (via the Systems Biology Graphical Notation (Le Novère et al. 2009) (http://www.sbgn.org/) e.g. via Arcadia (Villéger et al. 2010) (http://www.sourceforge.net/projects/arcadiapathways/). Armed with such networks, it is possible to analyse their dynamics and other properties using tools/ modelling environments such as COPASI (Hoops et al. 2006) (http://www.copasi.org/) and to compare model and experimental data, conveniently stored using SBRML (Dada et al. 2010). Models and attendant metadata are best stored directly in databases, such as that set down in the B-Net database model (see Li et al. 2003; Mehrotra et al. 2010) as used in our yeast model (Herrgård et al. 2008) (http://www.comp-sys-bio.org/yeastnet).

Interrogating the model

Sensitivity analysis

Armed with a model, there are a number of important studies that are usefully performed. The first is the study of the contribution of individual steps to the control of the variables of interest. This is the domain of local and global sensitivity analysis (Saltelli et al. 2004, 2008), to which we have made significant contributions (e.g. Lüdtke et al. 2008; Sahle et al. 2008; Yue et al. 2006, 2007, 2008). Sensitivity analysis studies the quantitative contribution of individual steps to the overall control of a process. The ‘local’ version has been popularised in biochemistry as ‘metabolic control analysis’ (e.g. Fell 1996; Heinrich and Schuster 1996; Kell and Westerhoff 1986a), and, for instance COPASI (Hoops et al. 2006) calculates the control or sensitivity coefficients directly from a model. The results of these kinds of analyses are represented by a rank order of the most important reactions or parameters, which provides an important starting point for the combinatorial analysis of these complex networks. Formalisms such as Metabolic Control Analysis also explain why the modulation of individual steps singly rarely has much of an effect on an overall pathway (see e.g. Pérez et al. 2009a, b), reviewed by Gems (Gems and Doonan 2009), for a typical example.

Combinatorial analysis of parameter sensitivity

As indicated above, it is commonly the case in complex biochemical networks that while changes in individual parameters have little effect on the behaviour of biochemical pathways—indeed evolution is thought to have selected for robustness to individual parameter changes (Bornholdt and Sneppen 2000; Kitano 2007; Lehár et al. 2008; Morohashi et al. 2002; Stelling et al. 2004; Wagner 2005)—combinations of parameter changes can and do have major effects. A straightforward corollary of this is that in order to cause or inhibit the progression of diseases—including inflammatory diseases such as asthma (Biswas and Rahman 2009; Bowler 2004; Bowler and Crapo 2002; Boyer and Liu 2004; Chodaczek et al. 2007; Ciencewicki et al. 2008; Comhair and Erzurum 2010; Galli et al. 2008; Greene 1995; Han et al. 2001; Horváth et al. 1998; Jarvis et al. 2005; Kocyigit et al. 2004; Muñoz et al. 2009; Narula et al. 2007; Nemery 1990; Pae et al. 2008; Riedl and Nel 2008; Shore 2008; Vlašić et al. 2009)—it is necessary to affect multiple steps simultaneously. The problem is to find which ones, and that is a combinatorial problem that scales poorly. It is exactly here where the ability to interrogate a suitable model of the pathway comes to the fore, since computations to determine which combinations of parameters to affect can be done enormously more rapidly than can ‘wet’ experiments. To be explicit, if manipulating (let us say knocking out) just three genes out of 1,000 is necessary to secure a desired effect (as is often the case) and the question is to choose which three, the answer involves recognizing that this is a combinatorial optimization problem involving ca 100 million combinations—a trivial number computationally given a model and an easy number (i.e. 3) to work with post hoc, but an implausible number to interrogate with present experimental methods. See (Park et al. 2007, 2008) for a nice example of the approach.

At all events, the results of running a systems biology model in the forward direction are the time-varying concentrations of variables that result from the network topology and parameters of the system, and these can then be compared with measured variables to see how accurate the model is.

Of course it is typically the case (i) that the variables predicted by the model differ from those that one has measured, and (ii) one has only measurements of the variables and not the parameters anyway. Since it is the parameters that determine the system behaviour, it is then necessary to try and estimate or infer the parameters of the systems from measurements of the variables, the domain of inverse modelling (Liu and Wang 2008; Mendes and Kell 1996) or system identification (Bongard and Lipson 2005; Ljung 1987).

Inverse modelling

Finding the sets of parameters that can reflect a set (or sets) of variables is a much harder problem. If there are just 20 parameters, each of which can take just 10 values, there are at once 10^{20} combinations, although there may be multiple combinations that give a reasonable solution (the problem or system is then said to be under-determined). At all events, finding these combinations requires methods that can effectively search these combinatorial search spaces to find good solutions (they are not provably optimal solutions as these kinds of problems are NP-hard, Garey and Johnson 1979).

There are many kinds of approaches to attacking these kinds of combinatorial optimisation problems, and I give two examples. The first uses evolutionary methods to modify the search for these parameters, while the second is Bayesian in character.

Evolutionary computing methods (e.g. Bäck et al. 1997; Goldberg 1989, 2002) use ideas from Darwinian evolution to select and modify parameters to achieve a desired objective (or objectives—this is known as multi-objective optimisation, Handl et al. 2007). In an evolutionary algorithm, one selects a population of models encoding a different candidate set of parameters, assesses their performance, rejects those that perform poorly and modifies the parameters of the better-performing models using methods akin to recombination and mutation to create a second generation population and so on. Finally, one finds a candidate set of solutions that perform well and can indeed interrogate these solutions to determine the parameters that differ most frequently in the selected solutions from those in the starting pathway. These kinds of methods are recognised as highly effective (Banga 2008; Banga and Balsa-Canto 2008), and they have proved so for both modelling (Dada and Mendes 2009; Mendes and Kell 1998; Moles et al. 2003; Rodriguez-Fernandez et al. 2006) and other optimisation problems (e.g. Broadhurst et al. 1997; Kell et al. 2001; Knight et al. 2009; O'Hagan et al. 2005, 2007; Platt et al. 2009; Rowe et al. 2010). A related and novel approach that we have developed (Wilkinson et al. 2008) (and see Brown et al. 2010) also evolves estimates of parameters, but in a somewhat different way. Evolutionary computing methods are amenable to ('coarse-grained') parallelisation that allows them to run on many (hundreds or even thousands of) processors simultaneously, and we have used this approach with great effectiveness (Wedge and Kell 2008; Wedge et al. 2009). Overall, the result of this kind of approach is the effective determination of the multiple parameters that are required to explain the system variables.

A conceptually quite different approach, which may of course be expected to lead to the same result (and which in consequence strengthens further any conclusions from e.g. an evolutionary computing approach), is an approach based on Bayesian inference (Jayawardhana et al. 2008; Liebermeister and Klipp 2006; Vyshemirsky and Girolami 2008) and known as Markov Chain Monte Carlo or MCMC. In this approach (which we do not rehearse in detail as those details have recently been published by us, Jayawardhana et al. 2008), we have knowledge of the variables of interest and sample candidate models that can explain those variables using various estimates of their parameters *from a distribution*. The MCMC algorithm then slowly builds up the likeliest values of the parameters and their possible distribution given the demonstrable uncertainty.

Detecting the modes or sites of action of a toxin

Clearly, if we have measurements of the variables of a system before and after the addition of a toxin, we can estimate the parameters in the two cases and see which have most plausibly changed by applying these inferencing methods to the two cases. This automatically gives the mode(s) or site(s) of action of the intervention, whether of a toxic inhibitor or by any other means. In other words these methods can detect the modes or sites of action of anything that causes a system to change its state. Taking the Bayesian approach (see also e.g. Nidhi et al. 2006; O'Hagan 2006; Vyshemirsky and Girolami 2008; Wilkinson 2007), in the work described above (Jayawardhana et al. 2008) we 'calibrated' our approach using purely simulated data in which we knew exactly which parameters had been changed (and in which direction) and showed that we could detect this accurately. We then applied our approach to an experimental system of metabolic engineering in *Lactococcus lactis* (Hoefnagel et al. 2002) where the investigators had manipulated the activity of a specific enzyme to achieve a desired metabolic effect. Our approach detected both the enzyme whose activity had been modified and suggested the site of another significant pleiotropic effect (these always occur, Featherstone and Broadie 2002). Thus, the power of this general approach is that it is free of specific hypotheses and thus guides us to the hypotheses that can best explain the data. These are classic data mining methods (e.g. Breiman 2001; Kell and King 2000; Kell and Oliver 2004; Wu et al. 2008) that allow us to discover mechanisms of action that are unknown and/or have not previously been contemplated. Note, however, that such methods need careful handling from a statistical point of view (e.g. Altman and Royston 2000; Broadhurst and Kell 2006; Hastie et al. 2001; Ioannidis 2005, 2008). A variety of other network inferencing methods also exist (e.g. Lorenz et al. 2009; Managbanag et al. 2008; Stolovitzky and Califano 2006; Stolovitzky et al. 2009).

Why most toxins will have multiple sites of action

A variety of means are available for testing these mechanisms further, including the use of modulation of the expression of constituent parts of the proposed pathways by genetic means (e.g. Jones et al. 2007), and in particular the use of appropriate iron chelators and antioxidants, alone or (preferably) in combination. The combinatorial aspect is important, since there are theoretical grounds, as well as abundant evidence, to the effect that several steps in a network must be modulated *simultaneously* to exhibit substantial effects (see e.g. Ágoston et al. 2005; Ambesi-Impiombato and di Bernardo 2006; Bender et al. 2006; Borisy et al. 2003; Csermely et al. 2005; Dancey and Chen 2006; Fan et al. 2003, 2006; Haggarty et al. 2003; Hopkins et al. 2006; Kaelin 2005; Keith et al. 2005; Kostoff and Delafuente 2006; Millan 2006; Perlstein et al. 2006; Sharom et al. 2004; Shiomi et al. 1999; Wermuth 2004) (Brötz-Oesterhelt and Brunner 2008; Chong and Sullivan 2007; Costanzo et al. 2010; Gerber et al. 2007; Goltsov et al. 2009; Hegreness et al. 2008; Huang et al. 2008b; Jia et al. 2009; Koufaki et al. 2009; Kuhn et al. 2010; Lee et al. 2007; Lehár et al. 2007, 2008a, b; Li et al. 2007; Liby et al. 2007; Morphy and Rankovic 2007; Pachauri et al. 2009; Reznichenko et al. 2010; Sarkar and Li 2009; Sarkar et al. 2009; Sawyers 2007; Schrattenholz and Šoškić 2008; Silver et al. 2009; Silver 2007; Sporn et al. 2007; Stommel et al. 2007; Suchy et al. 2009; Ulrich-Merzenich et al. 2009; Watterson et al. 2008; Weinreb et al. 2009b; Whitehurst et al. 2007; Wong et al. 2008; Yeh et al. 2006, 2009; Ying et al. 2008; Zamin et al. 2009; Zhang 2006; Zhang et al. 2010; Zimmermann et al. 2007). The same holds true for biotechnology (Kell and Westerhoff 1986a), in which typically we seek to maximise fluxes (Park et al. 2007, 2008). Of course some molecules—both nutrients/natural products and pharmaceutical agents—can act as both antioxidants and iron chelators; these are likely to be especially useful in minimising the damage from toxicants of many kinds.

Concluding remarks

Science consists of both analysis and synthesis, and thus a substantial amount of Science involves finding regularities (‘Laws’) that can be extracted from observables, even when some of those observables or their presumed causes seem to have little in common (Kell and Oliver 2004; Oldroyd 1986; Westerhoff and Kell 2007). Thus, there are many kinds of toxins that can cause death or injury, but it is not necessarily obvious what they share in terms of their modes of action. What I have therefore sought to do here is to bring together the evidence for the autocatalytic involvement of poorly liganded iron (leading, *inter alia*, to hydroxyl radical formation) in a considerable number of these. Certainly the exact molecular mechanisms, cascades and networks involved in each case depend on many other factors, and appropriate systems biology methods can tell us what they are, but I would argue that the extensive evidence for iron’s involvement that I cite here and elsewhere (Kell 2009a) is very hard to ignore. Hence, the view that iron is the nexus.

Acknowledgments I thank a great many colleagues and correspondents for their contribution to the refinement of my thinking about these issues, and Julie Cowley for assistance with literature, etc. Previous work that has led to this review has been funded by the BBSRC, EPSRC and MRC.

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