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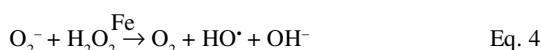
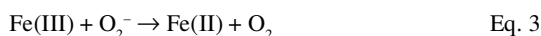
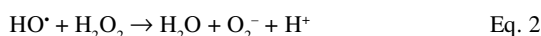
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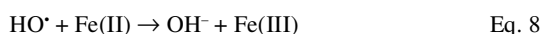
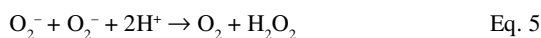
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In a recent review published in this journal,¹ Koppenol traced the history of the Fenton reaction and of the catalytic decomposition of H₂O₂ by iron salts. If his purpose was to shed light on current understanding of related chemistry in biological systems, he failed. Moreover, he managed to sow confusion by inaccurate reporting of the work of others. What follows is an attempt to point out these shortcomings and thus to clarify the situation.

The Fenton reaction (Eq. 1) is the reduction of H₂O₂ by Fe(II); in combination with two other reactions (Eqs 2 & 3), it explains the catalytic decomposition of H₂O₂ by Fe(II) as first presented by Haber, Weiss, Wilstätter and Barb *et al.*^{2–4} The sum of Equations 1 and 3 (Eq. 4) has been called the Haber-Weiss reaction.



The chain length of the process described by Equations 1–3 is limited by chain termination steps such as Equations 5–8.



Equation 4 does not occur in the absence of the catalytic metal (Fe or Cu). This reaction has been referred

to as the iron-catalyzed Haber-Weiss reaction, or as superoxide-driven Fenton chemistry. The term Fenton-catalyzed Haber-Weiss reaction, mentioned by Koppenol, should be avoided, since it is not correct. At present, whenever the term Haber-Weiss reaction is used it is understood to occur under the catalytic influence of iron. When first used to explain why the decomposition of methional to ethylene was dependent upon both O₂^{•−} and H₂O₂,⁵ the catalytic role of the metal was not appreciated because the phosphate buffer used contained the needed Fe. The role of Fe was soon clarified.^{6,7} We and others have discussed this previously.^{8–12} Haber, Weiss, Wilstätter^{2,3} and Barb *et al.*⁴ were the discoverers of this chemistry.

Koppenol stresses that Equation 4 does not occur in the absence of metal catalysis. That fact was known half a century ago,⁴ and has been confirmed repeatedly since then.¹¹ He also avers that the Haber-Weiss reaction (Eq. 4) has no biological significance and that only the Fenton reaction (Eq. 1) is toxic. Surely the Haber-Weiss reaction (with iron catalysis) has been demonstrated *in vitro* in biochemical systems numerous times.^{6,7,10–13} In non-reducing environments, such as these *in vitro* reactions, the Haber-Weiss reaction has reality and is deleterious due to the production of the potent oxidant HO[•], or its equivalent Fe(II)O or Fe(III)OH. However, it has long been appreciated that Fe in the reducing environment of the cytoplasm would be maintained in its Fe(II) state leaving no role for Equation 3.¹⁴

Yet an *in vivo* toxic synergism between O₂^{•−} and H₂O₂ was made obvious from the enhanced H₂O₂ sensitivity of SOD-null mutants.¹⁵ This has been explained on the basis of the rapid oxidation of the [4Fe–4S] cubane clusters of dehydratases, such as dihydroxy acid dehydratase, fumarases A and B, and aconitases, by O₂^{•−}. This

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univalent oxidation causes release of Fe(II) from these enzymes and that Fe(II) then participates in the Fenton reaction (Eq. 1). We proposed this mechanism¹³ and it was soon verified by Imlay and his students¹⁶ and further relevant work has been reviewed.^{8–10,17} Koppenol makes no mention of any of this; preferring to leave the neophyte reader uninformed and confused.

He also confused the history that he did present. Thus Koppenol denies that Willstätter, Haber, and Weiss participated in the discovery of the mechanism of the Fenton reaction. His reason for this statement being partially that Haber and Weiss did not mention Fenton. However, they first proposed Equation 1³ and that is indubitably the Fenton reaction. Moreover, Haber and Willstätter² first proposed Equation 2 while Barb *et al.*⁴ established the significance of Equation 3 for the overall process of the iron-catalyzed decomposition of hydrogen peroxide. Koppenol also misquoted a statement in our previous review.¹⁰ We¹⁰ did credit Haber, Weiss, Willstätter and Barb *et al.*^{2–4} for the discovery of the mechanism of the decomposition of H₂O₂ by iron salts. All these workers thus contributed to our appreciation of this process. So, does the Haber-Weiss reaction (Eq. 4) have any biological significance? In the reducing environment of the cytoplasm surely not. But, in extracellular fluids where oxidants can exceed reductants, it is certainly possible.

In this,¹ his most recent review, Koppenol reverses a strongly stated former opinion.^{18,19} Thus to quote from an earlier review:¹⁸ 'it may be in order to retire the Fenton reaction. After its discovery more than 100 years ago, and its important role in biochemistry for nearly 30 years, a rest is well deserved'. No reason for this changed view is given. Koppenol advises the reader never to mention the Haber-Weiss reaction again. Many catalyzed reactions that we speak of frequently do not proceed at measurable rates in the absence of catalysis. One O₂^{•−} does not react directly with another without catalysis. What we see in the absence of catalysis at neutral pH is due to the O₂^{•−} + HO₂[•] reaction.²⁰ Should we not mention the dismutation of O₂^{•−} on that account?

In a similar vein, one H₂O₂ does not react directly with another to give O₂ + 2H₂O; one needs catalysis by catalase or by some metal cation. Surely Koppenol's admonition to the reader cannot be taken seriously. Thus Equation 4 is not a non-reaction, as it is called by Koppenol. It is rather a catalyzed reaction. Koppenol does correctly point out that the accepted name for this reaction (Eq. 4) does not acknowledge the contribution of Willstätter. It also does not acknowledge the contribution of Barb *et al.*⁴ who contributed to the modern view; but a name that acknowledged all those deserving of recognition would be unwieldy and nomenclature is often unfair. Thus the Fenton reaction (Eq. 1) was actually formulated by Haber and Weiss.³ We are in a real sense stuck with those names for to change them now, after years of frequent usage,

would be confusing to our descendants. A name is required for the *in vivo* process whereby O₂^{•−}, acting as an oxidant, causes release of Fe from the [4Fe–4S] clusters of dehydratases and that Fe then reduces hydroperoxides. Rather than a cumbersome name memorializing contributors we propose '*in vivo* superoxide-driven Fenton chemistry'. We use the term chemistry rather than reaction, because peroxides other than H₂O₂ may be involved.

Science is a cumulative process. Explanations that are reasonable when formulated are properly discarded when new data make them untenable. No good purpose is served by polemical reviews that flog theories that have long been superseded. That is particularly the case when the more recent views, and the data that support or contradict them, are not mentioned.

CONCLUSIONS

What then is our understanding ~70 years after the Fenton and Haber-Weiss reactions were first proposed? Should we even be discussing the chemical significance of those reactions given that the chemistry was resolved half a century ago? Yes, because this chemistry is central to the vibrant field of free radical biology. Thus more than 30 years ago it was suggested that O₂^{•−} and H₂O₂ synergise in producing a powerful oxidant, possibly HO[•], which could explain the importance of the superoxide dismutases. Scores of papers have confirmed the reality of such a synergism both *in vitro* and *in vivo* and have established a role for iron in this synergism. The 'Haber-Weiss reaction', or '*in vivo* superoxide-driven Fenton chemistry', explains these phenomena. Fenton chemistry, which can involve organic peroxides as well as H₂O₂, is biologically relevant both through O₂^{•−}-driven and O₂^{•−}-independent routes; while the biological importance of O₂^{•−} involves more than driving Fenton chemistry; but that is outside the scope of this discussion.

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