Oxidants and human disease: some new concepts[1]

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ABSTRACT

Oxidant species such as superoxide radical ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($HO\cdot$), and lipid peroxides (LOOH) are becoming increasingly implicated in human disease. However, the question of whether such oxidants are a major cause of tissue injury in human disease or are merely produced during such injury has been difficult to answer because of inadequate experimental techniques, and possibly because of an overemphasis on lipid peroxidation as a mechanism of oxidant injury. Recent developments in methodology, in our understanding of the primary mechanism of oxidant toxicity to cells, and in concepts of antioxidant protection are reviewed. Good evidence now exists for some role of oxidant damage to tissues in the pathology of several human diseases, including rheumatoid arthritis, reperfusion injury, immune injury to lung and kidney, and cerebral trauma or ischemia. These have led to promising suggestions for new therapeutic approaches.— HALLIWELL, B. Oxidants and human disease: some new concepts. *FASEB J.* 1: 358-364; 1987.

Key Words: oxidants • tissue injury • superoxide radical • hydrogen peroxide • hydroxyl radical • lipid peroxides • antioxidants

A FREE RADICAL IS ANY SPECIES capable of independent existence that contains one or more unpaired electrons, i.e., electrons present singly in atomic or molecular orbitals. An unpaired electron can be associated with almost any atom, and some examples of biological relevance are given in Table 1.

The free radical field is a large, multidisciplinary research area (1-5). For example, the basic chemistry of superoxide ($O_2^{\cdot-}$) and hydroxyl ($HO\cdot$) radicals was determined many years ago by radiation chemists; the outline mechanism of lipid peroxidation was elucidated by scientists at the British Rubber Producers Association; combustion is a free radical reaction; and some of the most detailed chemical work on peroxidation and antioxidants has been carried out in the food industry and by polymer scientists.

In 1954, Gershman and Gilbert proposed that most of the damaging effects of elevated O_2 concentrations on living organisms could be attributed to the formation of free radicals (reviewed in ref 5). However, this idea did not capture the interest of many biologists and clinicians until the discovery in 1968 of an enzyme that is specific for the catalytic removal of a radical (2). That enzyme is, of course, superoxide dismutase (EC 1.15.1.1) (1, 2). The pioneering work of McCord and Fridovich (2, 6) has led to many fundamental discoveries, including the fact that phagocytes use $O_2^{\cdot-}$ and H_2O_2 to aid bacterial killing (3); an understanding of why some lactobacilli accumulate manganese ions and of how toxins such as paraquat, alloxan, and 6-hydroxydopamine damage cells; and new knowledge of microbial adaptations during transitions from anaerobic to aerobic life (1, 4-6). Superoxide dismutases, together with enzymes that remove H_2O_2 [catalase (EC 1.11.1.6) and glutathione peroxidase (EC 1.11.1.9)], are the major intracellular antioxidant defenses of mammalian cells. GSH-dependent enzymes are also involved in protection against lipid peroxidation.

Interest in the role of free radicals and hydrogen peroxide (which is not a radical; see Table 1) in toxicology and human disease grows daily; Table 2 provides some of the conditions in which the involvement of oxygen-derived species ($O_2^{\cdot-}$, H_2O_2, $HO\cdot$) has been suggested. The purpose of the present article, which is based partly on a recent symposium (7), is to report some current developments in our understanding of free radical biology, and to evaluate the likelihood of using our present knowledge to develop effective disease therapies.

OXIDATIVE STRESS: THE ROLE OF METAL IONS

Oxidative stress in cells and tissues usually refers to increased generation of $O_2^{\cdot-}$ and H_2O_2. This can be achieved by *1)* raising O_2 concentrations (sometimes inadvertantly; culture of most mammalian cells under 95% O_2 or even under air exposes them to higher O_2 concentrations than those in vivo, *2)* adding certain toxins that increase intracellular oxidant formation (such as alloxan, paraquat, or adriamycin), or *3)* activating a large number of phagocytes [$O_2^{\cdot-}$ and H_2O_2 are produced by activated phagocytes and are essential for the killing of many bacterial strains (3), but they can do tissue damage when generated in excess].

[1]This review is based partly on the proceedings of a meeting on oxidants and disease, sponsored by the Upjohn Co. and held in Kalamazoo, Michigan, USA, April 1987 (see ref 7).

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TABLE 1. *Types of free radical wtih biological relevance*

Type of radical	Examples	Comments
Hydrogen-centered	H atom (1 proton, 1 electron)	H atom abstraction from carbon often initiates radical chain reactions, e.g., HO· can initiate lipid peroxidation by abstracting H from the fatty acid side chains of membrane lipids: L–H + HO· → L· + H_2O
Carbon-centered	Trichloromethyl radical, CCl_3·; carbon-centered radicals in membrane lipids formed by H abstraction (L·)	Major agent in CCl_4 toxicity
Sulfur-centered	Thiyl radical, R–S·	Reactive radical produced during oxidation of thiol compounds (accelerated by transition metals)
Nitrogen-centered	Phenyldiazine radical, $C_6H_5N=N$·	Involved in phenylhydrazine toxicity to erythrocytes
Oxygen-centered[a]	Inorganic	
	Superoxide ($O_2^{\cdot -}$)	Important agents in oxidative stress: hydroxyl very reactive, superoxide poorly so
	Hydroxyl radical (HO·)	
	Organic	
	Alkoxy radicals (LO·)	Produced during peroxidation by reaction of L· with O_2 (LO_2·) and by metal-dependent decomposition of lipid peroxides (LO· and LO_2·); any carbon-centered radical usually reacts quickly with O_2 to yield peroxy radicals (4): e.g., CCl_3· + O_2 → O_2CCl_3· (trichloromethylperoxy radical)
	Peroxy radicals (LO_2·)	
Transition metal ions	Cu^+/Cu^{2+}	Ability to accept and donate single electrons makes them important catalysts of free radical reactions (see Table 3)
	Fe^{2+}/Fe^{3+}	
	Ti(III)/Ti(IV)	

[a] O_2 itself is a radical; the diatomic oxygen molecule has two unpaired electrons. Hence one-electron reduction of oxygen gives $O_2^{\cdot -}$ (one unpaired electron) and two-electron reduction gives H_2O_2 (no unpaired electrons). Thus H_2O_2 does not qualify as a radical, although its ability to generate HO· makes it an important oxidant (see text).

Neither $O_2^{\cdot -}$ nor H_2O_2 is very reactive, so how can they produce injury? Both can find targets within certain cells at which they can do direct damage. Thus $O_2^{\cdot -}$ inactivates *Escherichia coli* dihydroxy-acid dehydratase (EC 4.2.1.9), and H_2O_2 inactivates spinach chloroplast fructose-bisphosphatase (EC 3.1.3.11) (1, 6; see paper by Fridovich in ref 7). However, a major mechanism of H_2O_2 toxicity in oxidant stress is the formation of a highly reactive species in the presence of suitable transition metal catalysts; this species is most likely the hydroxyl radical HO·, although other reactive species may also exist (1, 8, 9). Metal ion-dependent formation of HO· from H_2O_2 is accelerated by the presence of $O_2^{\cdot -}$ or, under certain circumstances, of ascorbic acid (8).

HO· combines with most biological molecules at rates that are almost diffusion-controlled. Because of its extreme reactivity, HO· must react at or close to its site of formation. It follows that an important determinant of the nature of the damage done to cells and tissues by oxidant stress is the location of metal ion complexes capable of accelerating HO· formation (8, 9). Indeed, a general feature of the participation of transition metal ions in radical reactions is that they convert poorly reactive species into more reactive ones (Table 3). Thus autoxidation of thiols, diphenols, and ascorbic acid produces reactive radicals, but these autoxidations depend on traces of contaminating metal ions. Lipid peroxides decompose under physiological conditions in the presence of iron or copper ions to generate highly cytotoxic aldehydes (10). Of such aldehydes, malondialdehyde (sometimes called malonaldehyde, or MDA) receives the most attention, yet it is now known to be relatively poorly toxic (10).

Iron ions seem to be the likeliest promoters of radical reactions. Hence one must ask, what iron complexes are available in vivo to stimulate damaging radical reactions, such as HO· formation? Biochemists spent considerable time in the 1970's and early 1980's looking for "iron promoters" of radical reactions in human and animal body fluids (8). It is now clear that organisms have evolved to keep transition metal ions safely sequestered in storage or transport proteins as much as possible. Indeed, metal sequestration is an important part of extracellular antioxidant defenses (9). However, cells do contain a small low-molecular-mass iron pool, which supplies iron for the synthesis of ferroproteins. Exactly where this pool is in the cell is not clear, but it is probably largely compartmentalized into a vacuole (8). Its existence may explain why superoxide dismutase and H_2O_2-removing enzymes are such important intracellular antioxidants; it is vital to remove as much $O_2^{\cdot -}$ and H_2O_2 as possible before they come into contact with this low-molecular-mass iron pool (8, 9). Unfortunately, oxidant stress can *create* more metal promoters of radical reactions. Thus, $O_2^{\cdot -}$ can release iron from ferritin (11) and H_2O_2 degrades

TABLE 2. *Clinical conditions in which the involvement of oxygen radicals has been suggested*[a,b]

Inflammatory-immune injury
Glomerulonephritis (idiopathic, membranous)
Vasculitis (hepatitis B virus, drugs)
Autoimmune diseases
Rheumatoid arthritis

Ischemia — reflow states
Stroke/myocardial infarction
Organ transplantation
Inflamed rheumatoid joint?

Drug and toxin-induced reactions

Iron overload
Idiopathic hemochromatosis
Dietary iron overload (Bantu)
Thalassemia and other chronic anemias treated with multiple blood transfusions
Nutritional deficiencies (kwashiorkor)

Alcoholism
including alcohol-induced iron overload

Radiation injury

Aging
Disorders of premature aging

Red blood cells
Phenylhydrazine
Primaquine, related drugs
Lead poisoning
Protoporphyrin photoxidation
Malaria
Sickle cell anemia
Favism
Fanconi's anemia

Lung
Cigarette smoke effects
Emphysema
Hyperoxia
Bronchopulmonary dysplasia
Oxidant pollutants (O_3)
ARDS (some forms)
Mineral dust pneumoconiosis
Bleomycin toxicity
SO_2 toxicity

Heart and cardiovascular system
Alcohol cardiomyopathy
Keshan disease (selenium deficiency)
Atherosclerosis
Adriamycin cardiotoxicity

Kidney
Autoimmune nephrotic syndromes
Aminoglycoside nephrotoxicity
Heavy metal nephrotoxicity

Gastrointestinal tract
Endotoxin liver injury
Halogenated hydrocarbon liver injury (e.g., bromobenzene, CCl_4, halothane)
Diabetogenic action of alloxan
Pancreatitis
NSAID-induced gastrointestinal tract lesions
Oral iron poisoning

Brain/nervous system/neuromuscular disorders
Hyperbaric oxygen
Vitamin E deficiency
Neurotoxins
Parkinson's disease
Hypertensive cerebrovascular injury
Neuronal ceroid lipofuscinoses
Allergic encephalomyelitis and other demyelinating diseases
Aluminium overload
Potentiation of traumatic injury
Muscular dystrophy
Multiple sclerosis

Eye
Cataractogenesis
Ocular hemorrhage
Degenerative retinal damage
Retinopathy of prematurity
Photic retinopathy

Skin
Solar radiation
Thermal injury
Porphyria
Hypericin, other photosensitizers
Contact dermatitis

[a] The explosive growth of interest in free radical reactions has prompted the establishment of two journals: *Free Radical Research Communications* and *Free Radical Biology and Medicine*. Both are recommended as a source of interesting papers in this area. [b] NSAID, nonsteroidal antiinflammatory drug; ARDS, adult respiratory distress syndrome.

the heme of hemoglobin to liberate iron ions (12). Even then, the availability of iron to stimulate radical reactions is very limited; preliminary attempts to measure catalytic iron concentrations in extracellular fluids by the bleomycin method (see paper by Gutteridge in ref 7) gave values of 5 μM or less, even at sites of intense inflammation where there is extensive generation of $O_2^{\cdot-}$ and H_2O_2 by activated phagocytes, and other bleeding, that liberates hemoglobin (8, 9). The iron-binding proteins transferrin (present in plasma) and lactoferrin (secreted by neutrophils) are far from saturated with iron in vivo (except during iron overload), and can bind metal ions liberated from other proteins, thus helping to diminish damaging radical reactions (9).

As pointed out by Borg (paper in ref 7) and others (8, 9), experimenters studying radical reactions such as lipid peroxidation in vitro often add 50–200 μM concentrations of iron complexes. This amount is grossly unrepresentative of the situation in vivo, where the rate of formation of HO· (from H_2O_2) or cytotoxic aldehydes (from lipid peroxides) may be limited not by the supply of $O_2^{\cdot-}$, H_2O_2, or lipid peroxide, but by the availability of metal ions (9). Thus undecomposed H_2O_2 and lipid peroxides can easily be detected in vivo (13, 14).

However, cellular injury appears to increase the availability of metal ions, perhaps by interfering with their storage in vacuoles (if such storage is energy-dependent) or simply by causing vacuolar lysis. Thus, once cellular injury has begun, damaging radical reactions tend to be amplified. A striking example, of potential therapeutic relevance, occurs on traumatic damage to the brain or spinal cord. Certain areas of the brain are rich in iron, and cerebrospinal fluid has no significant iron-binding capacity. Hence, injury to the brain causes release of metal ions that stimulate lipid peroxidation (8, 9). This lipid peroxidation may contribute to postinjury tissue degeneration, and attempts to use antioxidants and metal chelators to prevent it have given encouraging results in animal model systems of stroke and of brain injury by skull impact (7).

TABLE 3. *Role of metal ions in converting less reactive to more reactive species*

$O_2^{\cdot-}$, H_2O_2	Fe/Cu[a]	HO·
Lipid peroxides (ROOH)	Fe/Cu[b]	RO· (alkoxy), RO_2· (peroxy), cytotoxic aldehydes
Thiols (RSH)	Fe/Cu plus O_2[c]	$O_2^{\cdot-}$, H_2O_2, thiyl (RS·), HO·
NAD(P)H	Fe/Cu plus O_2[c]	NAD(P)·, $O_2^{\cdot-}$, H_2O_2, HO·
Ascorbic acid	Cu/Fe[d]	semidehydroascorbate radical, HO·, H_2O_2, degradation products of ascorbate
Catecholamines, related autoxidizable molecules	Fe/Cu/Mn plus O_2[c]	$O_2^{\cdot-}$, H_2O_2, HO·, semiquinones (or equivalent radicals derived from the oxidizing compounds)

[a]The iron- or copper-catalyzed Haber-Weiss reaction: $H_2O_2 + Cu^+ (Fe^{2+}) \rightarrow HO\cdot + OH^- + Cu^{2+} (Fe^{3+})$. [b]Lipid peroxide decomposition is metal ion-dependent, and eventually produces highly cytotoxic products such as 4-hydroxy-2,3-*trans*-nonenal, and less toxic ones such as malondialdehyde (10). [c]Most so-called autoxidations are stimulated by traces of transition metal ions, and proceed by free radical mechanisms. [d]Copper ions are especially effective in decomposing ascorbic acid, and ascorbate/copper or ascorbate/iron mixtures are cytotoxic.

OXIDATIVE STRESS: THE MOLECULAR TARGETS

Early events in mammalian cells subjected to oxidative stress, e.g., by adding a bolus of H_2O_2 or by using toxins such as alloxan (which leads to increased intracellular formation of $O_2^{\cdot-}$ and H_2O_2), seem to be DNA damage and consequent activation of poly(ADP-ribose) synthetase, an enzyme that polymerizes ADP-ribose residues from NAD^+ (15–18). These events are associated with depletions of nicotinamide and adenine nucleotides, and rises in intracellular Ca^{2+} concentrations (15–21).

Figure 1 shows how these processes may be related. DNA that has been carefully purified to free it of metals reacts very slowly, if at all, with $O_2^{\cdot-}$ or with H_2O_2 in vitro. Hence the DNA damage in vivo may be due to a site-specific generation of HO· upon the DNA itself. This means either that the DNA has transition metal ions bound to it in vivo, or that the oxidative stress liberates such metal ions that rapidly bind to the DNA. Analysis of isolated DNA for products of HO· attack on purine and pyrimidine bases could be used to test this proposal of site specificity (22).

Activation of poly(ADP-ribose) synthetase as a result of DNA strand breakage by HO· will deplete nicotinamide nucleotides within the cell (15, 18), concurrently with an increased demand for NADPH as GSH is oxidized by the action of glutathione peroxidase on H_2O_2. Decreases in the concentrations of NAD(H), NADP(H), GSH, and ATP, combined with the fact that cellular Ca^{2+}-sequestering mechanisms are sensitive to direct inactivation by oxidants (23), may produce rises in intracellular Ca^{2+} and possibly similar rises in cytosolic transition metal ions, which lead to amplification of radical reactions (Fig. 1).

Of course, the primary target of oxidative stress need not always be DNA; it may differ from cell to cell and organism to organism. However, Ames (13) measured human urinary excretion of two products that apparently result from radical attack on DNA (thymine and thymidine glycol) and concluded that in normal humans, an average of more than 10^3 "oxidative hits" on DNA occur per day for each cell in the body. This supports the proposal that DNA is a major target of oxidant attack in vivo. Oxidative damage to proteins may also be important in vivo (e.g., dihydroxy-acid dehydratase, discussed previously) and oxidatively modified proteins can be recognized as abnormal by cellular proteolytic systems (24).

THE STATUS OF LIPID PEROXIDATION

Pioneering studies of the toxicity of carbon tetrachloride (CCl_4) to liver provided clear evidence for metabolism

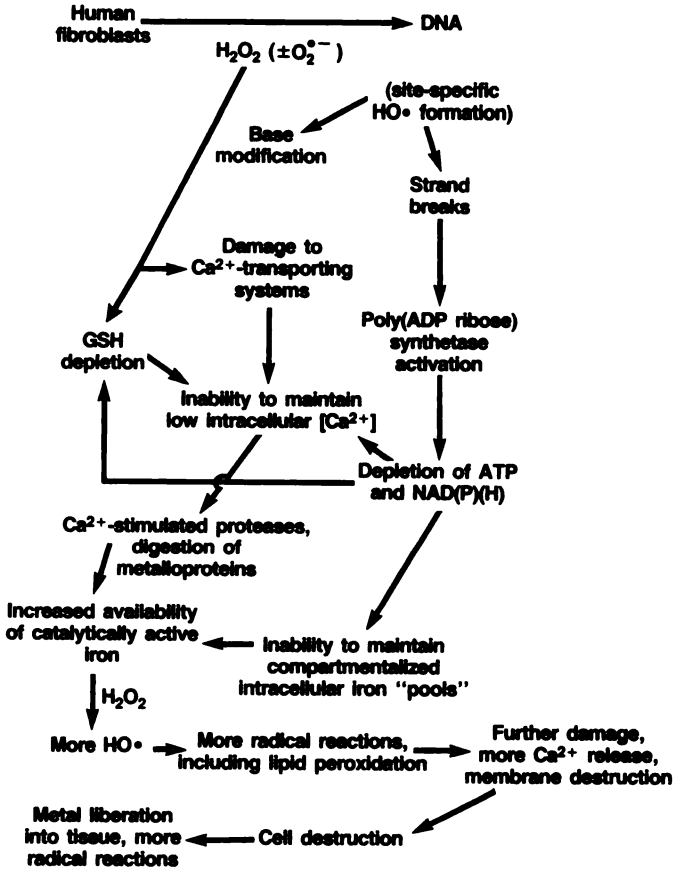

Figure 1. Interrelationship of oxidant damaging mechanisms.

of CCl_4 to free radicals ($CCl_3\cdot$ and $O_2CCl_3\cdot$; Table 1) that can initiate lipid peroxidation (4). This peroxidation plays a part in the hepatotoxicity of CCl_4, and "antioxidants" that inhibit peroxidation offer some protection against this liver damage (4). These impressive studies, combined with the availability of simple techniques for measuring end products of lipid peroxidation in tissue extracts and body fluids, focused attention on lipid peroxidation as a cause of cellular damage during oxidant stress.

More recent studies (15, 16, 19, 20) suggest that for most toxins induction of lipid peroxidation is *not* the mechanism by which they initially produce cell damage. Thus paraquat and diquat injure cells by increasing intracellular formation of O_2^- and H_2O_2, yet lipid peroxidation occurs at a late stage in the injury process and contributes little to it (16, 20). Figure 1 shows how oxidant injury by other mechanisms can lead, by GSH depletion and metal ion release, to lipid peroxidation as a late event, perhaps occurring only at the point of cell death and membrane lysis. Indeed, lipid peroxidation end products, measured by some of the newer assay techniques (13, 14), may be good markers of cellular injury during diseases such as rheumatoid arthritis (8), because they occur as a consequence of such injury rather than being the cause of it (25). Hence measurement of lipid peroxidation end products may be an index of cell destruction, somewhat like measurement of release of creatine phosphokinase or lactate dehydrogenase. Increased amounts of lipid peroxidation end products can probably be detected in almost any disease state, because cells and tissues damaged by any mechanism may peroxidize more rapidly than normal (Fig. 1). Thus the finding of increased end products of lipid peroxidation in tissues or body fluids in any disease provides no evidence that free radicals have anything to do with the origin or progress of that disease.

Another problem is that the techniques that are currently most popular for measuring lipid peroxidation end products are flawed. Application of the diene conjugation assay to human body fluids measures a UV-absorbing product that may not arise by lipid peroxidation (26). The thiobarbituric acid test not only is subject to interference (25), but also, in measuring malondialdehyde, fails to record the most cytotoxic aldehydic end products of lipid peroxide decomposition (10, 27).

However, lipid peroxidation, even if a late stage in cellular injury (Fig. 1), could be important in spreading injury to adjacent cells, as appears to be the case in postischemic or postinjury brain degeneration (discussed previously; also reviewed in ref 7). How true is this of other conditions? The lipid peroxidation inhibitor α-tocopherol (vitamin E) has been tested in several human diseases. Both vitamin E and other peroxidation inhibitors have also been tested in animal model systems of human disease, usually with disappointing results. Marked protective effects are seen only in cases where tissue vitamin E levels are low, as in retrolental fibroplasia and inborn errors of fat metabolism (28). Giving extra vitamin E does not confer much if any protection on vitamin E-replete subjects. Indeed, if lipid peroxidation is only a late stage in, say, paraquat-induced lung injury, then there is no reason to expect inhibitors of lipid peroxidation to protect the lung (reviewed in ref 16). However, evidence is accumulating for a link between lipid peroxides and atherosclerosis (29).

OXIDANTS AND HUMAN DISEASE

The precise role played by radicals and H_2O_2 in such disorders as rheumatoid arthritis or in immune injury to the kidney and lung is not yet fully clear, but they are formed and they interact with prostaglandins, leukotrienes, interleukins, and other modulators of immune function. Only collaborative research by scientists aware of all these factors will clarify the situation. Thus lipid peroxidation is linked to the cyclooxygenase pathway (14), O_2^- is involved somehow in neutrophil chemotaxis (7), and both platelet-activating factor and tumor necrosis factor modify oxidant production by phagocytes (7). Oxidants are also involved in T lymphocyte activation (7).

The diseases in which studies of oxidant mechanisms have come closest to offering new therapeutic advances are probably postinjury degeneration of the brain and spinal cord (as discussed above) and reoxygenation injury on reperfusion of ischemic tissues (7, 30). Ischemia itself injures cells, and will kill them if continued for a sufficiently long period. However, reperfusion after a brief period of ischemia, although beneficial in the long term, gives an initial insult to the tissue on reoxgenation that involves O_2^- and H_2O_2. These species do some direct damage, but also interact with metal ions released in the ischemic tissue to form $HO\cdot$ (7, 8, 30). Reoxygenation injury has been demonstrated not only in heart and brain, but also in skin, intestine, and pancreas (30), and it may occur in inflamed rheumatoid joints (31). Lucchesi et al. (see ref 7) emphasized the importance of protecting against reoxygenation injury during streptokinase infusion or other thrombolytic therapies, and in the preservation of organs for transplantation. Sources of O_2^- and H_2O_2 in tissues reoxygenated in vivo include xanthine oxidase (EC 1.1.3.22) (30) and activation of phagocytes infiltrating the reperfused tissue (7). As expected (Fig. 1), injury by these oxidants interacts in a complex way with changes in Ca^{2+} compartmentalization and products of arachidonic acid metabolism from phagocytes.

THERAPEUTIC POTENTIAL OF ANTIOXIDANTS

As mentioned above, antioxidants acting only as inhibitors of lipid peroxidation are unlikely to be generally successful in protecting against oxidant stress in disease or toxicology, although they may be very useful in the therapy of posttraumatic central nervous system injury and in the rare cases of poisoning by halogenated hydrocarbons (4). Whether they would protect against halothane hepatotoxicity or the development of atherosclerosis remains to be established.

Superoxide dismutase has been proposed as an antiinflammatory agent for use in rheumatoid arthritis, yet the

limited data published have not convinced many rheumatologists of its efficacy (32). Superoxide dismutase may be more useful in minimizing reoxygenation injury to tissues (30). The key role of H_2O_2 in cytotoxicity (Fig. 1) suggests that Ebselen, a low-molecular-mass agent with glutathione peroxidase activity (reviewed in ref 33), may have therapeutic potential, as may agents (such as methyl esters of GSH) that maintain intracellular GSH concentrations (34).

If one knows the source of the oxidants causing damage, a good approach is to block it. Thus allopurinol, an inhibitor of xanthine oxidase, protects tissues against reoxygenation injury as effectively as does superoxide dismutase (30), and is very much cheaper. Oxypurinol may have even more therapeutic potential, because it is not only a xanthine oxidase inhibitor but also a radical scavenger (35). Excessive oxidant production by activated phagocytic cells is important in several diseases (e.g., some forms of the adult respiratory distress syndrome) and inhibition of it might be therapeutically useful (36). Yet another approach has been to bind transition metal ions by using chelating agents that stop them from participating in radical reactions (8, 9). This approach, first proposed in 1979 with desferrioxamine as the chelating agent, has given promising results in several animal models of human diseases (reviewed in ref 9), but its application to humans awaits the development of more suitable chelating agents. Chelators such as 2,3-dihydroxybenzoate (9, 16) may have more therapeutic potential than very strong metal chelators such as desferrioxamine. Inasmuch as cell damage by oxidants may involve changes in GSH and Ca^{2+}, perhaps the best approach would be a combination therapy. Thus Lucchesi et al. (see ref 7) reported that inhibitors of arachidonic acid metabolism, Ca^{2+} chelators, and antioxidants all offered some protection against reoxygenation injury in the heart.

CONCLUSION

In recent years, scientists aided by new methodology (14, 16, 22, 27) have begun to identify the specific molecular targets of oxidant attack in cells, and studies of lipid peroxidation have been complemented by studies of oxidative damage to DNA (13, 22) and to proteins (24, 37). The interaction of oxidant injury with other mechanisms of cellular injury is now becoming clearer (Fig. 1). Just as, for example, Ca^{2+} may be involved in oxidant injury, so radicals may play some role in injury initiated by completely different mechanisms. These radical reactions, arising as a consequence of cell injury, may be important in some disease states but trivial in others. Hence the mere demonstration of increased end products of lipid peroxidation in diseased human tissues is not evidence that oxidants caused the disease, or even that they contribute significantly to its pathology. However, good evidence exists for a major damaging role played by oxidants in some disease states (e.g., reoxygenation injury, posttraumatic degeneration in the brain, and rheumatoid arthritis), which gives promising indications of new therapeutic approaches. FJ

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