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INVITED REVIEW
FREE RADICALS IN DISEASE PROCESSES: A COMPILATION OF CAUSE AND CONSEQUENCE

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INTRODUCTION

During the past forty years free radicals have been implicated in a large number of diseases, often with the unspoken assumption they substantially contribute to the primary cause of the disease. When we published our Lancet article "Lipid peroxidation, oxygen radicals, cell damage, and antioxidant therapy" in 1984[1], and proposed that most of the reports implicating lipid peroxidation in human diseases were better explained by the sequence shown below (in which lipid peroxidation occurs mainly as a consequence of cell damage), it was considered by many as highly provocative.

Disease or toxin	⟶	Cell damage or death	⟶	increase lipid peroxidation	(1)

Today, it is widely accepted that, in most cases, free radicals are a complicating component of disease pathology arising to a major or minor extent as a consequence of the underlying disease process.

Over one hundred diseases, in which free radicals have been implicated, have been grouped in this compilation under eight different headings to indicate how free radicals might have arisen. The groupings are intended to be flexible as multiple classifications may often apply.

1 Diseases involving the excessive production of superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl), by activated phagocytic cells.
2 Disease processes involving the increased formation of oxygen radicals by drugs and toxins.
3 Disease processes involving the transfer of electrons to oxygen by transition metals.
4 Diseases involving the abnormal oxidation of substrates, or changes in oxygen concentration.
5 Diseases involving a failure, or excessive consumption, of protective defences.
6 Diseases in which free radicals might arise through structural perturbation of the cell.

ABBREVIATION: ROS: reactive oxygen species, SOD: superoxide dismutase, XDH: xanthine dehydrogenase, XOD: xanthine oxidase, TBARS: thiobarbituric acid reactive substances, RBC: Red blood cell, PUFA: Polyunsaturated fatty acid, GSH: Glutathione reduced form

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7 Tissue damage by high or low energy radiation.
8 Radical complications of gene defects (not listed in 1–7 above).

Where possible useful reviews and seminal references are cited. The reviewer apologises to the many scientists who have contributed greatly to our knowledge of free radicals in disease processes, but whose work is not cited here due to the brevity of the presentation.

1 Diseases involving the excessive production of O_2^-, H_2O_2, and HOCl by activated phagocytic cells.

DISEASE	COMMENTS	REFS
Asbestosis	Iron content of asbestos fibres appears to contribute to tissue damage by catalysing free radical damage.	2,3
Alzheimer's disease	Senile plaque cores maybe enriched with aluminium and silicon. Al may accelerate radical damage in the presence of iron under certain circumstances.	4,5,6
Adult respiratory distress syndrome	Disturbance in iron metabolism, and evidence of oxidative damage to lipids, proteins and DNA. Patients treated with high oxygen concentrations.	7,8,9
Asthma	Inflammatory cells found in asthmatic airways.	10,11
Behcet disease (Uveitis)	Inflammation of the uvea and retinal vasculitis reported to respond to treatment with SOD in animal models.	12,13
Crohn's disease	Xanthine dehydrogenase (XDH) conversion to xanthine oxidase (XOD) may also contribute to ROS generation, as well as activated neutrophils.	14,15,16
Duodenal ulcer	Reoxygenation injury (see 4) and insults to the mucosa are suggested to cause neutrophil aggregation and activation, and subsequent oxidative damage.	17
Emphysema	Smoke radicals (cigarette) and toxins may damage anti-proteases which no longer control the activity of elastase.	18,19
Gout	Joint inflammation triggered by deposition of urate crystals.	20
Glomerulonephritis	Complement system activated through deposition of antigen-antibody complexes in glomeruli. Antibiotic gentamicin may also cause oxidant renal damage.	21
Haemodialysis	Neutrophil activation by contact of blood with dialysis membrane. Patients develop arthropathies with iron deposits in joints.	22,23
Kawasaki disease	Systemic angiitis. Treatment with SOD claimed to be more effective than aspirin.	24

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DISEASE	COMMENTS	REFS
Myeloperoxidase deficiency	Genetic disease. Phagocytic respiratory burst greater than normal but little or no HOCl produced. Rarely produces clinical symptoms.	25
Optic neuritis	Catalase and SOD reported to be anti-inflammatory in animal models.	26,27
Pneumoconiosis	Fibrosis of the lung and dyspnoea can result from dust inhalation and suggested free radical reactions.	28
Peripheral vascular disease	Increased susceptibility of red blood cells to lipid peroxidation possibly due to changes in membrane organisation.	29,30
Peyronie's disease	Plastic induration of the penis. Treatment with SOD claimed to modify the disease process.	31
Rheumatoid arthritis	Accumulation of activated neutrophils in the joint. Abnormalities reported in iron metabolism, antioxidant protection, proteolysis and reoxygenation.	32,33,34
Thermal injury	Heat-shock proteins are induced as part of a protective response along with phagocyte activation and TNF production.	35,36

2. Disease processes involving the increased formation of oxygen radicals by drugs and toxins

DISEASE	COMMENTS	REFS
Alcohol toxicity	Ethanol derived radicals, or oxidation products such as acetaldehyde, deplete cellular GSH. Acetaldehyde is also a substrate for XOD. Disturbances in iron metabolism. Antioxidant protection claimed in some animal models.	37,38
Doxorubicin toxicity (Adriamycin)	Redox cycling, iron-binding, DNA intercalating anthracycline antitumour antibiotic, causes cardiotoxicity.	39,40
Bleomycin toxicity	Iron-binding, redox cycling glycopeptide antitumour antibiotics, binds to DNA and cleaves fragments from the sugar (ie malondialdehyde) and bases.	41
Carbon tetrachloride (CCl_4) toxicity	Halogenated hydrocarbon, substrate for cytochrome P450 system, metabolised to trichloromethyl and trichloromethyperoxyl radicals.	42,43,44
Chargas' disease	Parasitic (Trypanosome cruzi) disease. Parasite lacks catalase and deficient in peroxidases. Trypanocide drugs exploit this weakness.	45

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DISEASE	COMMENTS	REFS
Diabetogenic agents	Alloxan and streptozotocin induce experimental diabetes by concentrating in β-islet cells of pancreas. Alloxan redox cycles to generate semiquinones and ROS.	46,47
Megaloblastic anaemia	Anaesthetic gas nitrous oxide (N_2O) can produce a macrocytic anaemia with evidence of vitamin B12 or folic acid deficiency. Reaction of N_2O with hydrated electrons (Eaq) can form $\cdot OH$.	48
Manganism	"Manganese madness" observed in manganese mine workers. Animal models show that Mn(III) complexes can oxidise catecholamines and decrease dopamine in the brain.	49
Malignant hyperthermia	Anaesthetic halothane can cause hyperventilation, tachycardia, limb rigidity and a fatal rise in temperature in susceptible individuals. Increased lipid peroxidation reported.	50
Methyl mercury toxicity	Organic mercury pollutant of ecosystems. Hg is a redox cycling metal. Homolytic cleavage releases methyl radicals ($\cdot CH_3$) and a mercury radical.	51
Oestrogen induced tumours	Redox active hormone producing semiquinones and ROS.	52
Parkinson's disease	Accelerated senescence of pigmented neurons in pars compacta of substantia nigra. Environmental toxins may be involved in development, free radicals may arise as a consequence of degeneration, involving disturbances in iron distribution.	53,54
Paraquat toxicity	Bipyridyl herbicide actively accumulates in lungs. Redox cycling structure generates ROS.	55,56,57
Sideroblastic anaemia	Accumulation of iron in erythroid cell mitochondria with impaired haemoglobin synthesis. Drug and toxin induced, can be genetic or acquired.	58
Spanish cooking oil syndrome	Olive oil adulterated with rapeseed oil and aniline. Lung damage and muscular wasting, 350 deaths, 20,000 affected in Spain. Role of free radicals not clearly established.	59

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3. Disease processes involving the transfer of electrons to oxygen by transition metals

DISEASE	COMMENTS	REFS
Colon cancer	Hypothesised that the high iron content of faeces and generation of ROS by bacteria produce OH and organic radicals which convert pro-carcinogens to proximate carcinogens.	60
Idiopathic haemochromatosis	Genetic disease. Iron-overload with non-transferrin bound redox active iron detected in plasma. Hepatomas may arise from ROS damage to DNA. Arthropathies common.	61,62
Iron poisoning	Serious form of childhood poisoning. Animal studies show severe tissue necrosis and formation of OH intragastrically.	63,64
Nickel toxicity	Ni complexes are potent sensitizing agents. Stimulation of lipid peroxidation and OH damage to DNA shown in model systems.	65,66
Ocular siderosis	Particle of iron in the vitreous gives reddish-brown or green discoloration to iris. PUFA's depleted, lipid peroxides formed in animal models.	67
Ocular haemorrhage	Intravitreal haemorrhage, with release of prooxidant haemoglobin. Retinal degeneration and blindness can occur.	68
Thalassaemia	Genetic disease. Transfusional iron-overload with redox active non-transferrin bound iron present in serum. Low levels of plasma vitamin E.	69,70,71
Wilson's disease	Genetic disease. Tissue copper overload due to failure to excrete copper in the bile. Low serum caeruloplasmin antioxidant activity.	72,73

4. Disease involving the abnormal oxidation of substrates or changes in oxygen concentration

DISEASE	COMMENTS	REFS
Alkaptonuria	Genetic disease with deficiency of homogentisate oxidoreductase. Homogentisate accumulates in tissue and can autoxidise to form semiquinones and ROS. Degenerative joint disease a common feature.	74

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DISEASE	COMMENTS	REFS
Cerebro vascular accidents	Increased serum levels of lipid peroxides reported (only as TBA-reactivity, however).	75,76
Diabetes mellitus	Chronic state of hyperglycaemia. Glucose autoxidation produces ROS. Serum levels of antioxidants, and peroxidation products suggest ongoing oxidative stress.	77,78
Dupuytren's contracture	Contracture of the fingers. Nodules contain increased substrates for XOD. Treatment with allopurinol claimed beneficial.	79
Frostbite	Tissue damage by freezing and thawing. Ischaemia followed by reoxygenation on thawing. Improvement claimed, in some animal models, with SOD and desferrioxamine.	80,81
Hypoxia	Oxygen insufficiency produces arterial tissue damage and the presence of TBARS in serum, artery, brain and liver. Xanthine dehydrogenase (XDH) is converted to XOD.	82,83,84
Hyperoxia	Normobaric oxygen breathed at concentrations greater than 21%. Increased pulmonary production of ROS. High PUFA containing tissues form lipid peroxides.	85,86
Hyperbaric oxygen	Oxygen breathed at a pressure greater than atmosphere. Increased formation of ROS.	87,88
Influenza	Increased level of XOD reported in tissue and extracellular fluids of mice. Treatment with SOD decreased mortality (data probably unique to mice).	89
Pre-eclampsia	Increased formation of serum lipid peroxides detected (only as TBARS, however).	90,91
Reoxygenation injury	Re-introduction of oxygen to tissues after a period of oxygen starvation. Applies to almost all organs and tissues. Multifactorial generation of ROS (XDH → XOD, prostaglandins, catecholamines, neutrophils, platelets, electron transport chains).	92,93,94
Shock syndromes	Increased lipid peroxidation products and decreased antioxidants reported. Precipitating factors include; cardiogenic, hypovolaemic, traumatic, apoplectic, septic, burns and endotoxin.	95,96

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DISEASE	COMMENTS	REFS
Sports anaemia and exercise stress	Increased oxygen consumption with increased ROS production during exercise. Redox active iron and copper excreted in sweat. Increased lipid peroxidation products reported in some animal studies.	97,98,99

5. Disease involving a failure, or excessive consumption, of protective defences

DISEASE	COMMENTS	REFS
Abetalipoproteinaemia	Genetic disease with failure to synthesise apoprotein B which prevents vitamin E absorption. Degenerative neurological complications can be treated with vitamin E.	100,101
Acatalasia	Genetic disease with low activities of catalase. Heinz body formation elevated, otherwise patients appear normal.	102
Amyotrophic lateral sclerosis	Degenerative disorder of motor neurons with 10% of cases known to be inherited. Tight genetic linkage found between familial ALS and mutations in a gene that encodes for CuZn SOD.	103
Atherosclerosis	Local thickening of artery intima with fibrous plaques which limit blood flow to vital organs. Oxidative LDL modification triggers macrophage uptake with formation of foam cells and plaque.	104,105
Ataxia telangiectasia	Genetic disease shows increased frequencies of spontaneous and radiation induced chromosomal aberrations and cancer.	106
Acquired immunodeficiency syndrome	Decreased level of GSH and other antioxidants reported. H_2O_2 has been shown to activate HIV expression in cells.	107,108
Bloom's syndrome	Genetic disease. Deficiency of DNA ligase I leads to failure to rejoin DNA. Increased cancel risk.	109
Cystic fibrosis	Genetic disease with over production of mucins. Extremely low levels of vitamin E with neurological symptoms similar to abetalipoproteinemia. Chronic respiratory tract infections lead to oxidative stress.	110,111
Down's syndrome	Genetic disease. Increased infection, heart defects and leukaemia risk. Tissue levels of CuZn SOD and lipid peroxidation products increased. Suggested that increased CuZn SOD imbalances oxidative damage.	112,113

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DISEASE	COMMENTS	REFS
Fanconi's anaemia	Genetic disease with increased cancer risk. Decreased RBC SOD activity and increased iron-loading of transferrin reported.	114,115
Friedreich's ataxia	Genetic disease. Skin fibroblasts are reported to show increased sensitivity to ionising radiation.	116,117
Glucose-6-phosphate dehydrogenase deficiency (Favism)	Genetic disease. Deficiency of glucose-6-phosphate dehydrogenase in RBC's which are unable to maintain normal levels of NAD(P)H. Inadequate detoxification of H_2O_2 resulting in haemolysis under oxidative stress eg vicia faba bean.	118,119
Glutathione peroxidase deficiency	Genetic disease. RBCs deficient in this enzyme resulting in mild haemolytic states, provoked by drugs such as sulfonamides.	120,121
Glutathione reductase deficiency	Genetic disease. Enzyme deficiency causes haemolytic anaemia and thrombocytopaenia. Provoked by oxidant drugs.	122
Glutathione synthetase deficiency	Genetic disease in which the enzyme is deficient resulting in a generalised glutathione deficiency.	123
Haemolytic syndrome of prematurity	Extremely low levels of plasma vitamin E. RBCs sensitive to haemolysis and peroxidation. Responds to vitamin E supplementation.	124,125
Haemolytic autoimmune anaemia (acquired)	Haemolytic disease resulting from an immune response to subject's own tissue antigens. RBCs susceptible to lipid peroxidation.	126
Intra ventricular haemorrhage	Haemorrhage in premature infants, reported to be reduced by vitamin E administration.	127
Kashin-Beck syndrome	Degenerative disease with arthropathies. Vitamin E and selenium claimed to be beneficial in early disease stages.	128
Kwashiorkor	Chronic malignant malnutrition. Antioxidant defenses seriously compromised with abnormalities in iron metabolism.	129
Keshan's disease	Selenium deficiency leading to fatal cardiomyopathies. The disease can be treated successfully with selenium.	130,131
Olivopontocerebellar ataxia	Genetic disease with reported low plasma and RBC vitamin E levels.	132

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DISEASE	COMMENTS	REFS
Oral contraceptives and cardiovascular risk	Oral contraceptives modify cellular and plasma antioxidants, and suggested to increase plasma lipid peroxides causing hyperaggregability.	133
Pancreatitis	Environmental factors and an aberrant function of hepatic cytochrome P450 enzymes are suggested to lead to ROS formation.	134,135
Retrolental fibroplasia	Retinal damage, sometimes leading to blindness caused by the use of hyperoxia in incubators for premature infants. Vitamin E supplementation reported to reduce eye and brain damage.	136,137
Xeroderma pigmentosum	Genetic disease in which DNA repair processes are defective. UV-light is dangerous to such patients causing skin cancers.	138
Trichothiodystrophy	Genetic disease in which DNA repair is deficient, but patients not prone to skin cancer. Cell culture studies suggest that xeroderma pigmentosum patients have low catalase activities whereas trichothiodystrophy cells have high catalase levels.	139

6. Disease in which free radials might arise through structural perturbation of the cell

DISEASE	COMMENTS	REFS
Aluminium toxicity	Behavioural disorders common. Synergism with iron in promoting lipid peroxidation. SOD activity decreased in animal models.	5,140
Benzene toxicity	Degeneration of the hemopoietic system with leucopaenia, aplastic anaemia and risk of leukaemia. Lipid peroxidation increased in animal models.	141
Cerebral trauma	Brain or spinal cord trauma increases lipid peroxidation and iron release. Antioxidants such as "Lazaroids" claimed to protect.	142,143, 144
Cadmium toxicity	Cadmium is an environmental pollutant and carcinogen. Reported to increase lipid peroxidation in animal models.	145
Corneal ulceration	Insult to the eye by; chemicals, infection, thermal, puncture, or vitamin A deficiency result in corneal melting. Animal models suggest ROS are involved, with invading phagocytic cells contributing to the damage.	146

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DISEASE	COMMENTS	REFS
Lead poisoning	Lead toxicity leads to anaemia by inhibiting haem synthesis. Reported to potentiate oxygen toxicity in rodents and accelerate lipid peroxidation.	147,148
Multiple sclerosis	Changes in serum and tissue lipid patterns reported, RBCs more susceptible to lipid peroxidation by hydrogen peroxide stress.	149,150
Muscular dystrophy	Duchenne's muscular dystrophy is a genetic disease. Inconsistent reports of changes in antioxidants and increased lipid peroxidation.	151,152
Neuronal ceroid-lipofuscinoses (Batten's disease)	Genetic diseases showing several forms. Deposition of ceroid and lipofuscin in tissues. Little or no evidence to support a primary role for lipid peroxidation.	153,154
Scleroderma	Clastogenic factors reported in plasma and other fluids. SOD reported to prevent damage by clastogenic factors. Clastogenic factors can arise as a result of poor storage or mishandling of samples.	155

7. Tissue damage by high or low energy radiation

DISEASE	COMMENTS	REFS
Cataractogenesis	Opacification of the lens by photo-oxidation of crystallin proteins. H_2O_2 levels are increased in the aqueous humour and GSH levels decreased in human cataractous lens.	156,157
Radiation cystitis	Inflammation of the bladder due to radiotherapy. Reported to be decreased by injection of SOD.	158
Melanoma	Skin cancer resulting from excessive exposure to UVB components of sun rays. The antioxidant hydroxyanisole has been successfully used as a depigmenting agent to treat melanomas.	159,160
Neonatal Hyperbilirubinemia	Photodynamic therapy involves irradiation with blue light, from a sunlamp, of infants developing jaundice soon after birth. Bilirubin sensitizes its own destruction involving singlet oxygen.	161
Photosensitivity	Phototoxic or photo allergic reactions. Many drugs can act as photosensitizers. Singlet oxygen is often involved as an oxidant along with O_2^- and H_2O_2 formation.	162,163

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DISEASE	COMMENTS	REFS
PUVA Therapy	Photosensitizing agents such as psoralens are used to treat skin diseases such as psoriasis, using ultraviolet light in the wavelength range 320–400 nm (UVA).	164
Radiation sickness	Since 70% of body mass is H_2O, whole body irradiation produces substantial yields of ·OH radicals. SOD and certain low Mr copper complexes have been claimed to offer radio-protection as do many thiol group-containing molecules.	165,166

8. Radical complications of gene defects not listed in 1–7 above

DISEASE	COMMENTS	REFS
Chronic granulomatous disease	Genetic disease in which phagocytosis is normal but neutrophils cannot mount an oxidative burst. The killing of some bacteria by ROS is defective.	167,168
Huntington's chorea	Genetic disease appears in middle age with massive accumulation of fluorescent pigment in the brain, accompanying degeneration of striatal tissue.	169
Progeroid syndromes	Genetic diseases. Hutchinson-Gilford (Progeria) and Werner's syndrome, together have many features of accelerated ageing. Increased levels of oxidatively modified proteins detected in fibroblasts.	170,171, 172
Sickle cell anaemia	Genetic disease producing haemoglobin S which polymerises at low O_2 tensions and generates ROS causing cell haemolysis. Non-transferrin bound iron often present in plasma along with low vitamin E concentrations.	173,174

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