Systemic Lupus Erythematosus and Other Autoimmune Diseases from Endogenous and Exogenous Agents: Unifying Theme of Oxidative Stress

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Abstract: Extensive evidence supports oxidative stress (OS) via endogenous and exogenous agents as an important factor in induction of autoimmunity. OS arises from the immune system and other endogenous sources. The literature contains support for OS involvement of various drugs and other exogenous substances that produce the condition. Studies reveal prevention or amelioration by antioxidants.

Keywords: Systemic lupus erythematosus, autoimmunity, xenobiotics, oxidative stress, antioxidants.

INTRODUCTION

There is mounting evidence for involvement of oxidative stress (OS) in the mechanism of physiologically active substances, including: anti-infective drugs [1], anticancer agents [2], carcinogens [3], reproductive toxins [4], nephrotoxins [5], hepatotoxins [6], and various others [7a]. The most common reactive oxygen species (ROS) are superoxide (SO), hydrogen peroxide, hydroxyl radical, and peroxyl radicals, which are often formed by electron transfer (ET). ET functionalities include quinones (or precursors), metal complexes (or chelators), aromatic nitro compounds (or reduction products) and imines (or iminiums), which may undergo redox cycling with oxygen to give rise to ROS. The preponderance of bioactive substances or their metabolites, including those associated with systemic lupus erythematosus (SLE), contain ET groups. OS can produce beneficial results, as with drugs, or unwanted side effects in the case of toxins. The mode of action is complex and probably multifaceted in many cases.

The literature contains little on the role of xenobiotics in SLE. In 1985, a free radical pathway was proposed for SLE entailing both endogenous causes, and, a small number of drug-mediated cases [8]. In 1996, a review [9] underlined the significance of OS involvement with endogenous agents and of inhibition by antioxidant defenses. Our contribution updates this approach for the endogenous class and also invokes OS as a unifying theme encompassing many xenobiotics, mainly drugs, which apparently emulate the immune system. Another review [10] tabulates more than 60 xenobiotics in the SLE category. Other SLE agents, not investigated here due to space limitations, may also display an OS component. In accord with the OS approach, the observation that symptoms usually disappear upon cessation of the offending drugs is noteworthy [10]. Undesirable side effects of other types are addressed elsewhere [3-7a].

ENDOGENOUS GENERATORS OF OS

Immune System

Knowledge of immune system operation is mandatory for an understanding of SLE. Phagocytes, of which, neutrophils are most numerous, and macrophages make up an important part of the immune response against invading organisms [7b]. The contribution of ROS in the activity of these endogenous bodies is well characterized. The phagocytic respiratory burst involving oxygen uptake is essential when discussing free radical production, immunity, and OS. In hypoxic environments, there is a large decrease in the effectiveness. An enzyme-mediated reduction of molecular oxygen generates SO, an important ROS precursor, which yields H_2O_2 from dismutation. The potent HO• and HOO• can also be generated, especially in the presence of Fenton catalysts; scavengers of HO• produced a loss in phagocytic protection. Myeloperoxidase-mediated formation of HOCl can lead to HO•. Immune cells also use reactive nitrogen species (RNS) and degradative enzymes in their activity.

Other Sources of ROS

Several enzymes in the cytosol of animals are known to reduce O_2 to SO, including xanthine oxidase and cytochrome P450s (CYP450) [7c]. Iron-containing heme complexes form SO via oxidation of Fe(II) to Fe(III). A chief source of endogenous ROS is the mitochondria since some leakage occurs along the ET chain forming SO. The endoplasmic reticulum, nuclear membrane, and certain bacteria are also implicated as producers of ROS.

Autoimmunity

Autoimmune (AI) responses and illnesses comprise processes whereby normal components of the body are adversely targeted by antibodies [10]. Whereas typical invading organisms are called antigens, these endogenous immune targets are often referred to as autoantigens. AI dysfunction is categorized as systemic or tissue specific. Systemic types involve targets throughout the body, whereas tissue specific ones entail attack of cellular constituents specific to the organ or body part. The prevalence in the western industrialized world is about 5%, mostly women. The etiology of such diseases is still largely unknown.

SLE, rheumatoid arthritis, and scleroderma comprise the common forms of systemic AI disease, symptoms of which include butterfly rash, photosensitivity, psychosis, arthritis,

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blood and DNA aberrations, and the presence of certain nuclear autoantigens and antinuclear antibodies. Of the more than 60 xenobiotics known to induce SLE-like syndrome, procainamide and hydralazine account for up to 40% of these cases. The tissue specific class involves organs or components such as thyroid, kidney, skin, red cells, platelets, and joints.

SLE is most recognized for the presence of a wide variety of antibodies in the serum of patients, of which, anti-doublestrand-DNA antibodies are the most specific and widely recognized [11]. Oxidation can lead to sister chromatid exchange and formation of 8-OH dG. Apparently, patients lack the ability to undergo repair [11,12,7d], although this view has been widely challenged. There have been various studies on the OS topic [13-19]. Nitric oxide is known to play a role [20-25]; OS and ET mediated by nitric oxide have been reviewed [26]. Relevant is discussion in the section on Prevention and Amelioration by AOs.

METABOLISM, OS, AND ET

Aromatic Amines

Metabolism entails oxidation to hydroxylamine, nitroso, and nitro derivatives, all of which potentially operate as ET agents. The first two can redox cycle to generate ROS. Evidence supports participation of the ArNHO• radical [27]. The hydroxylamine can alkylate DNA via the nitrenium ion, which can lead to OS [2]. Also, nuclear hydroxylation forms phenolic precursors of ET quinones.

Aromatic Nitro Compounds

Metabolic reduction produces nitroso, hydroxylamine, and amine products. ET can occur with the parent and by redox cycling of ArNO and ArNHOH.

Quinone Precursors

Quinones and hydroquinones can undergo redox cycling with production of ROS via semiquinones. Aromatic hydrocarbons and phenols act as precursors upon enzymatic oxidation.

Metal Complexes and Chelators

Many drugs function as chelating agents to generate metal complexes that then operate in an ET mode, as discussed in the introduction.

DNA Alkylation

Hypotheses concerning the sources of OS have been discussed [2], in which iminium (see Introduction) from DNA alkylation may function in ET.

DRUGS [10] AND SLE-LIKE SYNDROME

Aromatic Amines

1. Procainamide

Studies of procainamide, p-$H_2NC_6H_4CONH(CH_2)_2NEt_2$, suggest that metabolites play a role [28-30]. Stepwise oxidation leads to the following derivatives: hydroxylamine, nitroso, and nitro (see Metabolism). All three products are potential ET agents. Individuals with high levels of the enzyme N-acetyl transferase exhibit protection from SLE, presumably from blockage of oxidation [30]. Data pointed to the hydroxylamine moiety as the active metabolite [28-30], evidently via enhanced generation of ROS. On the other hand, the nitroso derivative was found to be more toxic to lymphocytes than the hydroxylamine counterpart, suggesting that the nitroso may also play a part [31]. Generally, aromatic nitroso compounds display reduction potentials favorable for in vivo ET [32].

2. Dapsone

The major class used in the treatment of leprosy is the diaryl sulfone type. Dapsone, 4,4'-diaminodiphenyl sulfone, which inhibits PABA incorporation into folic acid, is the most active of this category [1]. An appreciable body of evidence indicates participation in oxy radical generation. A number of reports deal with in vivo or in vitro conversion to the N-hydroxy derivative and possibly to the nitroso form. There is evidence for involvement of oxidative phenomena including generation of SO and hydrogen peroxide by the hydroxylamino form in vitro.

Hydrazines

Hydralazine (**1**) is used to treat hypertension and high blood pressure [4]. The antidepressant phenelzine (phenethyl hydrazine) and the parent hydrazine also fit into the category of SLE-like syndrome. Similar to hydrazines in general, **1** is oxidized to ROS (SO, H_2O_2) and RNS in the presence of heme proteins and transition metal ions. This class increases lipoperoxidation. Metabolic studies performed with monosubstituted derivatives support the route shown in Fig.

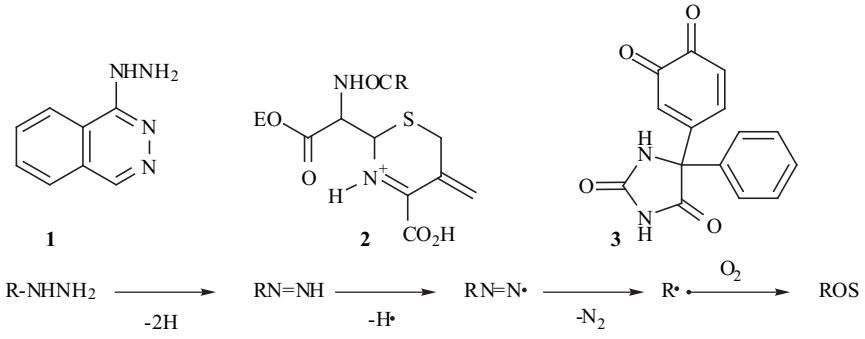

Fig. (1). Metabolism of hydrazines.

(**1**). In an oxygen environment, the carbon radical readily serves as a precursor for ROS by reaction with O_2, which could be responsible for the observed DNA scission. Alternatively, evidence exists for a DNA alkylation pathway.

Isoniazid

The isonicotinic hydrazide is best known as an antitubercular drug. Many modes of action have been proposed [5], most of which entail interference with NAD^+ and the ET system. Extensive metabolism, leading to free radical intermediates, gives rise to lipid peroxidation and DNA damage (see Hydrazines). The drug exhibits a high affinity for metals, particularly copper, which may result in ET reactions. Toxic manifestations in patients are alleviated by AOs. A referee points out that this SLE-like sydrome is rare, and doubts the reality of a causal association.

Azo Dyes

This class is best known for use as drugs in rheumatoid arthritis and inflammation. Toxicity conceivably arises through metabolic reductive cleavage to aromatic amines, which may be the active agents (see Aromatic Amines) [5]. Alternatively, the parent compound might function as an ET agent. Thus, azo compounds act as electron acceptors to form radical anions, which can then generate SO by donating electrons to oxygen. For amino azo dyes, a good correlation was observed between carcinogenicity and radical generation. Lipoperoxidation was elicited by metanil yellow and orange II. Olsalazine [33] and sulfasalazine [10], both associated with SLE, can be reductively cleaved to aminosalicylic acid, which also gives rise to SLE [34]. All three compounds have functionalities capable of forming metal chelates that are potential ET agents.

Tetracyclines

It is hypothesized that the anti-infective action involves reversible binding to subunits of bacterial ribosomes, consequently affecting the attachment of tRNA molecules that are necessary for protein synthesis. Various findings point to involvement of ROS in the drug and toxic actions [5]. The agents can chelate metal ions. Complexes from iron and copper ions have been found to generate hydroxyl radicals from hydrogen peroxide, which can then damage carbohydrates and DNA. In addition, membrane lipid peroxidation is induced in the presence of metal ions.

Aminoglycosides

Familiar members of this anti-infective class are streptomycin, associated with SLE, and gentamycin. Radical species likely play a role in the toxic effects [1]. There has been controversy about whether a free-radical mechanism is involved because aminoglycosides are considered to be redox-inactive. However conversion into a redox-active form may occur, which can undergo ET with molecular targets. Aminoglycosides act as chelating agents by binding to metal ions such as iron, with subsequent induction of ROS and lipid peroxidation. Hydroxyl radicals from hydrogen peroxide may affect mitochondrial function since catalase has been found to inhibit alterations in mitochondrial respiration in vitro. There is a decrease in gentamicin-induced lipid peroxidation in the kidney upon administration of vitamin E, supporting the proposal of radical involvement.

β-Lactam Antibiotics

There is widespread acceptance that the major antibacterial action of β-lactams is dependent upon inhibition of cell wall enzymes [1]. However, a questioning of this oversimplified view can be found in the literature. Recently, the iminium hypothesis of β-lactam action was proposed entailing ET reactions, which occur after site binding. As applied to bicyclic types, usually lactam ring opening generates a basic imine that can form iminium upon protonation (**2**). An example is cephalosporin, identified with autoimmune hematological disease. Isomerism of the nonconjugated imine in the case of penicillin, an SLE inducer, was addressed in a computational approach. A number of investigators have examined the relationship between β-lactams and metals in living systems. In the presence of ferric and cupric salts, several types of penicillin are able to generate ROS. Radicals are formed in high yield in reactions between penicillin and hydrogen peroxide.

Nitrofurans

This class, best known for anti-infective properties, induces kidney tumors [5]. The metabolic transformations are well documented and enjoy broad consensus as being involved in bioactivity. Various lines of evidence point to generation of the radical anion which may be an important player. A correlation is observed between electron affinity and radio-sensitization, hypoxic cell toxicity, and chronic aerobic toxicity, suggesting that redox processes play an important role. In an aerobic environment the intermediate nitro radical anion readily conveys an electron to oxygen. For example, nitrofurantoin, an SLE inducer, stimulated the uptake of oxygen in hepatic incubations, which was partially reversed by SOD and catalase; this suggested the presence of superoxide and H_2O_2. Activated oxygen may be responsible for toxic effects. In other cases, including anaerobic conditions, the radical anion exerts its effect by another route, presumably interference with normal ET. Both the favorable effect and the liabilities might be intimately related to the ease of ET.

Phenytoin (Diphenylhydantoin)

This barbiturate finds use as an antiepileptic. It is proposed that the neurotoxin may act, in whole or in part, by imposing OS [4]. Metabolism of phenytoin yields phenol and catechol derivatives. Significantly, subsequent facile oxidation can form the quinone (**3**), which can produce ROS by redox cycling and binding to protein. The drug is known to generate oxidative damage to DNA and protein. Alternatively, an epoxide metabolite has been suggested as the agent responsible for adduct formation by way of alkylation, and may also function as a phenol precursor. Other hydantoins also induce SLE, e.g., mephenytoin.

Phenothiazines

An appreciable number of phenothiazine derivatives, e.g., chlorpromazine, find use as tranquilizers, antipsychotics, and antihistamines. This heterocycle interferes with energy production and induces autoxidative cell injury in connection with toxicity [4]. Relatively stable radical cations are generated by one-electron oxidation. Phenothiazines, which are photosensitizers, induce photo-oxidative damage to the skin due to generation of ROS, e.g., OH•, H_2O_2, and singlet oxygen. Chlorpromazine is believed to mediate neurotoxicity by an OS route. Since metabolism entails hydroxylation, ET quinones and redox cycling may arise via phenolic intermediates.

α-Methyl-Dopa

The drug, effective in reducing high blood pressure, exhibits side effects, including SLE [7e]. Microsomal oxidation, presumably by SO when NADPH is present, gives rise to quinones and semiquinones [7f]. These transformations are common for this catechol class. Membrane binding occurs, perhaps by attack involving sulfhydryl groups of protein. Another pathway entails interaction with GSH.

L-Dopa

Metabolism of the Parkinsonian drug is analogous to that of α-methyl-dopa. ROS can be formed by autoxidation, and also, via interaction with metals, e.g. copper, resulting in OS and DNA damage [7g].

Griseofulvin

This antibiotic, which also exhibits antifungal properties, appears to bind to RNA and subsequently interferes with microtubule movement and spindle formation. Lipid peroxidation has been observed after administration [1].

Penicillamine

The compound finds use as an antirheumatic and in treatment of Wilson's disease, acting as a copper chelator [4]. The drug readily chelates metals, conceivably with subsequent generation of ROS by ET with molecular oxygen. Also, thiols are known to function in a redox cycling capacity leading to OS, as recently reviewed [35].

Propylthiouracil (A) and Quinidine (B)

These lupus-inducing drugs, (A) antihyperthyroid and (B) antiarrythmic and antimalarial, are known to undergo myeloperoxidase mediated metabolism by stimulated neutrophils to ROS [36].

Cytokines

This class includes interferons (anticancer) and interleukins (anticancer, rheumatoid arthritis) which act as primers for macrophages leading to ROS [7h].

Cocaine

Cocaine intake produces various adverse effects [5]. In relation to metabolism, a minor route, apparently responsible for some of the toxic manifestations, consists of demethylation to norcocaine, followed by oxidation to a nitroxide that can be reversibly associated with the reduced N-hydroxy derivative. The hydroxy form generates ROS and lipid peroxidation via redox cycling. The nitroxide reduces electrochemically at a favorable potential, which may permit ET in biosystems.

Allopurinol

Allopurinol finds use in situations that require AO type of activity. It is becoming more and more recognized that compounds commonly identified as AOs can also function as pro-oxidants under the appropriate conditions, e.g., high levels of OS. [7i,35]. This appears to be the case for allopurinol in its nephrotoxicity. There is increased lipid peroxidation and production of ROS, accompanied by decreased levels of SOD and catalase.

OTHER INDUCERS OF SLE-LIKE SYNDROME

Chromium

Various unwanted responses have been documented [5], wherein multiple valence forms appear to be involved. Chromate reacts with hydrogen peroxide to form hydroxyl radicals and can undergo redox cycling entailing ROS and ET participation. DNA damage results from base oxidation and strand cleavage. GSH plays a beneficial role pointing to a role for OS. The valence states, Cr (VI), Cr (V), Cr (III), and Cr (II) can apparently cleave hydrogen peroxide to hydroxyl radicals [7j].

Chlordane

Oxidative addition to the pesticide double bond yields an epoxide metabolite that conceivably produces OS by DNA alkylation (See Metabolism) [4]. There is implication of various ROS and in DNA cleavage. The adverse oxidative effects are attenuated by AOs.

Trichloroethylene

The haloalkene, a nephrotoxin, leads to several biotransformation products [5]. The major pathway is the CYP450 mediated oxidation forming an epoxide, Fig. (**2**). Which can alkylate DNA, bind lipids and generate OS. A minor pathway involves transformation via glutathione S-tranferase, Fig. (**3**), to a product that can also undergo oxidation to produce OS by DNA alkylation.

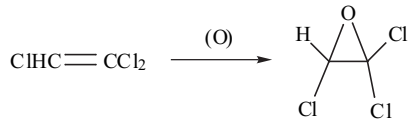

Fig. (2). Oxidation of trichloroethylene.

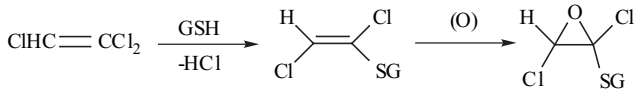

Fig. (3). Metabolism of trichloroethylene.

Radiation

For example, exposure to sunlight is known to exacerbate SLE. Ultraviolet light and other high-energy radiation are capable of generating radical entities from various cellular components [1].

Viruses

Viral infections have been associated with SLE-like syndrome. Both ROS and RNS play a complex role in viral infection and immune responses [1].

XENOBIOTICS [10] AND OTHER AUTOIMMUNE DISEASES

A number of agents listed under SLE are active in this category.

Hematological Diseases

Cephalosporin

See β-lactams.

Ibuprofen

The drug is an anti-inflammatory agent that also displays analgesic and antipyretic properties. As is often the case, metabolism has been linked to toxicity [5]. Decarboxylation is purported to yield a sec-carbon radical which can combine with oxygen to form a hydroperoxide. Subsequent decomposition provides the sec-alcohol end product. Toxicity is attributed to the ROS involved.

Phenacetin

As a result of dealkylation, the compound serves as a metabolic precursor of acetaminophen (AAP) which has been extensively investigated due to its widespread use as a pain reliever [5]. Metabolism and associated toxicity have been summarized [7k]. AAP, the N-acyl derivative of p-aminophenol, undergoes oxidation to the N-acetyl p-iminoquinone. GSH depletion is associated with high levels of AAP leading to increases in ROS. The common feature of lipid peroxidation in OS is also present. Toxicity appears to be multifaceted since enhancement in Ca and NO levels occurs.

Thyroid Diseases

Polychlorinated Biphenyls (PCBs)

Evidence for the crucial involvement of ET-OS in toxicity has been reviewed [4,37]. Metabolism, known to play an important role, entails hydroxylation as an important route. PCBs bind to nuclear receptors in rat liver extracts. The more linear or rectangular structures exhibit better affinity for the target. The relatively non-polar and lipophilic PCBs become affixed with appreciably lower strength than oxygen containing derivatives. For example, 3, 3', 5, 5'-tetrachloro-4,4'-dihydroxybiphenyl showed strong affinity for attachment. The corresponding tetrachlorodiphenoquinone exhibited remarkably greater binding activity, which comprises evidence for our proposition. The presence of an extended π system in a rigid planar configuration may be a dominant factor. In addition, m-chlorine substituents appear to play an important role. Recently, evidence was presented for metabolic conversion of PCBs to the corresponding quinone.

The scenario is further elucidated by reports on influence of the degree of conformational coplanarity of PCBs on binding and toxicity. The more coplanar molecules (less ortho substitution) readily attach to the receptor and are quite toxic, including tumor promotion. In contrast, less coplanar PCBs (more ortho substitution) have low affinity for the receptor, are less toxic, and are weak promoters. These findings correlate nicely with the ease of conversion to the diphenoquinone product which incorporates obligatory coplanarity and may be the active binding agent. It might be significant that the structural features that make for maximum binding also can promote ET. In relation to electrochemical characteristics, quite positive reduction potentials of +0.26 V and +0.39 V were reported for the quinone.

Our theoretical framework is in accord with another metabolic pathway, applicable to a significant number of PCBs, consisting of hydroxylation initially to phenols, followed by conversion to catechols. In turn, these can be further transformed to quinones and semiquinones, with ensuing redox cycling and binding to cell components via nitrogen and sulfur nucleophiles in 1,4-addition reactions.

There is considerable literature on OS arising from PCBs. Lipid peroxidation was observed in various animals based on malondialdehyde and ethane formation. The generated ROS could well be the underlying cause of toxicity. Although the precise source of activated oxygen is not known, redox cycling by quinone metabolites is a reasonable conjecture.

Renal Disease

Cadmium

Upon exposure to this toxin, depletion of GSH ensues due to induction of a pro-oxidant state [5]. Chronic administration resulted in lipid peroxidation which was attenuated by incorporation of ascorbate.

Mercury

Alkylmercury exposure results in ROS production and increased lipid peroxidation [5]. SO levels are enhanced by administration of Hg(II) which also appears to accelerate the Fenton reaction involving iron with resultant enhancement of lipid peroxides.

Paraquat

It is generally accepted that redox cycling leading to OS is responsible for toxic manifestations [5]. The favorable reduction potential gives rise to ROS, such as SO and

H_2O_2, as well as HO• which is believed to be responsible for DNA damage. Alleviation by AOs, e.g., Se and SOD, is in line with involvement of OS. The compound, a member of the iminium ET family and an herbicide, has been extensively investigated as a redox-cycling agent [7L].

Liver Disease [6]

Ethanol

Alcohol toxicity [5] is manifested mainly in the liver, CNS, and fetus, but less commonly in the kidney and SLE. During metabolism, the pathway proceeds via acetaldehyde to acetic acid with intermediate radical formation and accompanying ROS. Subsequent effects include lipid and protein oxidation. Macrophage activation with release of SO has been noted. As expected, AOs were able to counter the toxicity resulting from OS.

Halothane

The gas, 2-bromo-2-chloro-1,1,1-trifluoroethane, finds use as an anesthetic inhalant [7m]. Toxic side reactions include liver damage, in addition to SLE. Metabolism, giving rise to carbon radicals, can lead to peroxyl radicals by interaction with oxygen and subsequent lipid peroxidation. Some metabolites can form adducts by binding to protein.

Scleroderma

Bleomycin [2,44]

This clinically useful anticancer drug, a glycopeptide produced by organisms, has attracted considerable attention mechanistically. The in vivo reaction involves a sequence of iron chelation, oxidative activation, DNA binding, and DNA cleavage. The bithiazole constituent seems to be a binding contributor. Complexation, involving the ferrous state, is followed by covalent attachment to oxygen resulting in a ferric peroxy radical that is very short lived. Electron and proton uptake provide the more stable ferric hydroperoxide. Apparently, this oxidant is responsible for DNA chain scission entailing the sugar moieties. Although the latter stages are not as well elucidated, it is reasonable to invoke homolytic cleavage of the peroxyl bond to generate the highly reactive hydroxyl radical in close proximity to the sugar target.

Organic Solvents

These liquids are ubiquitous in the commercial arena, as well as in the laboratory and home. In many instances, inhalation due to volatility and skin penetration from dermal contact are prominent physical features. Voluminous studies have been performed with test animals. Some of the more important members are CCl_4, $CHCl_3$, CH_2Cl_2, trichloroethylene, benzene, aliphatic hydrocarbons, and glycol ethers. Various toxic effects have been addressed from the standpoint of OS, ROS, and ET with accompanying evidence [3-5].

Vinyl Chloride

Vinyl monomers make up an important class of commercial chemicals in the polymer industry. A common thread appears applicable to the mechanism [5], as discussed above for trichloroethylene.

Cisplatin

Cisplatin, $Cl_2Pt(NH_3)_2$, finds use in chemotherapy, but, as usual, toxicity enforces limits. The various modes of action have been critically analyzed [4]. There is widespread consensus that activity results from intra- and inter-strand cross-links that bend and unwind DNA, resulting in attractions of certain proteins with resultant interference with excision repair and other vital DNA processes. However, it appears that binding alone is not sufficient and that some mechanism which occurs after the Pt species attaches itself to DNA must account for the anticancer activity. Since considerable evidence indicates that many other metals operate by ET-OS, it is reasonable to propose a similar mode of action in this case. Appreciable support has appeared for this thesis which has attracted little attention. Involvement of radicals and lipoperoxidation have been observed in various systems accompanied by decrease in antioxidant levels. SO arises from interaction with DNA. Also, resistance to the drug is associated with increase in levels of GSH. Plausibility for this rationale is provided by recent reports that ROS are involved in the cytotoxicity which is enhanced by GSH depletion. In addition, cisplatin is known to activate macrophages. Electrochemical data lend additional credence to this chemical viewpoint. The drug induces apoptosis, which may arise from radicals generated in the vicinity of DNA. Cisplatin displays radiation sensitizer properties, which usually entail ET reactions. Free radical damage has been proposed for the nephrotoxicity which is ameliorated by AOs.

Disease or Response in Animals

Copper

A common involvement in OS is via the Fenton-type reaction with H_2O_2 or other hydroperoxides [5]. Complexes can lead to ROS resulting in 8-OH dG production from DNA. Free radical reactions evidently play a role in Wilson's disease, characterized by high levels of the metal.

PREVENTION AND AMELIORATION BY AOS

Various reports demonstrate positive effects of AOs versus SLE in humans and other animals. SOD and copper chelates that can destroy SO have proven helpful [7n]. A study [38], entailing vitamins C and E, and β-carotene revealed beneficial effects. A significant increase in serum 8-OH dG was detected in SLE patients, which may be lessened by vitamin C [39]. Other AOs in the form of thiols, such as cysteamine and N-acetylcysteine, suppressed immune damage [40]. High levels of ROS and low AO status have been implicated in the pathogenesis [41-43] (vide supra). Inclusion of AOs into the multi-modality therapy has been suggested [9,40]. Other references [9,22] incorporate relevant information. It is important that large-scale investigations of AOs be initiated so that the general population, as well as those afflicted, might benefit.

Other Mechanistic Considerations

Attempts have been made to discern structure-activity relationships (SAR) for SLE xenobiotics, but with little

success [10]. The present review provides a plausible SAR based on ability to induce OS, applicable to both endogenous and exogenous categories, thus, providing a broad unifying theme. There has also been discussion of "Which immunologic effector mechanisms are involved in the pathogenesis of autoimmune disease caused by xenobiotics" [10]? Our approach is very much in line with the conclusion, "Apparently, there are no major differences between the pathogenic mechanisms of xenobiotic induced and 'idiopathic' auto-immune disease" [10]. Other factors could contribute to the observation that patients with drug-induced lupus display much fewer immune perturbations than do SLE patients.

Regarding the aspect of individual differences, not all persons exposed to SLE xenobiotics develop the disease. Autoimmune responses elicited by the agents are likely regulated by various endogenous, genetically determined factors [45]. With reference to the OS hypothesis, inherent AO defenses, regular AO supplementation, or high AO diets could be factors in prevention (see the preceding section). It should be emphasized, as mentioned in the introduction, that the mode of action is complex. The situation is multifaceted with OS being only one of various important features.

ACKNOWLEDGEMENTS

We thank Ryan Peat for assistance and acknowledge support by the SDSU-MIRT Program under the direction of Dr. R.S. Pozos, NIH No. 5T37TW00067.

ABBREVIATIONS

AAP	=	Acetaminophen
AI	=	Autoimmune
AO	=	Antioxidant
ArNO	=	Aromatic nitroso
ArNHOH	=	Aromatic hydroxylamine
DNA	=	Deoxyribonucleic acid
CNS	=	Central nervous system
CYP450	=	Cytochrome P450 monoxygenase
ET	=	Electron transfer
GSH	=	Glutathione
NADPH	=	Nicotinamide adenine dinucleotide phosphate (reduced form)
NAD+	=	Nicotinamide adenine dinucleotide (deprotonated form)
8-OH dG	=	8-hydroxy 2'-deoxyguanosine
PABA	=	p-Aminobenzoic acid
PCB	=	Polychlorinated biphenyl
OS	=	Oxidative stress
NO	=	Nitric oxide
RNS	=	Reactive nitrogen species
ROS	=	Reactive oxygen species
SAR	=	Structure activity relationship
SLE	=	Systemic lupus erythematosus
SO	=	Superoxide
SOD	=	Superoxide dismutase
t-RNA	=	transfer-Ribonucleic acid

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