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REVIEW ARTICLE

Radiation-Protective Agents in Mammals

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CONTENTS

The protective effect of chemicals against the damaging action of ionizing radiation was first noted by Dale (1). A decrease in the inactivation of two enzymes by X-rays was brought about by the addition of several substances, including colloidal sulfur and thiourea, to aqueous solutions of the enzymes. Since then, radiation protection has been observed in a variety of animal and plant cells by a surprising number of compounds, albeit of relatively few chemical or pharmacological classifications. Chemical radiation protectors, it should be pointed out, are effective only when administered prior to exposure to radiation, and should therefore be considered distinct from substances, such as bone marrow cells, which are used for restorative therapy after irradiation.

Radioprotection of a bacteriophage was noted in 1948 by Latarjet and Ephrati, using thioglycolic acid, glutathione, tryptophan, cysteine, and cystine (2). Radioprotection of mice was achieved shortly after by means of cyanide (3), cysteine (4), and thiourea (5), these protective effects being attributed at the time to inhibition of, or reaction with, cellular enzymes. The importance of an amino group for the radioprotective action of a mercaptan was first shown by Bacq (6), who removed the carboxyl group of cysteine in order to liberate the basic function; this resulted in the important discovery of cysteamine (β-mercaptoethylamine), still regarded as one of the most potent of the radioprotective agents.

Since 1952, other types of structures have been found with radioprotective effects, including a number of commonly used pharmacological agents, but the most effective have generally been derivatives or analogs of the aminoalkyl mercaptans. Present research attempts have been more concerned with the explanation of radioprotection in the cells than the discovery of new protective agents, and a number of plausible explanations have been put forward. No wholly convincing evidence for any of the major postulated mechanisms of radioprotection has yet been described, but some cellular events appear quite reasonable in regard to the protection afforded by several of the more highly investigated compounds.

This review attempts to list the various types of

chemical structures for which some protection against the deleterious effects of ionizing radiation in mammals has been found. It should be recognized, however, that for many of the compounds included, testing results from only one laboratory have been reported; results from another laboratory or testing in another system may give quite different results. Detailed discussions of the action of the more widely accepted radiation-protective agents appear elsewhere; the purpose here is to catalog those structures with protective activity and describe the more widely considered mechanisms of protection by which they may act.

ANTIRADIATION TESTING

Most testing of antiradiation agents has employed X- or γ-rays from an external source. Neutrons have been infrequently used. Test animals are most often mice or rats, with guinea pigs used less frequently. Antiradiation testing with dogs or monkeys has been limited to the more effective compounds as determined from screening with mice or rats. Further information on this subject may be found in a number of texts devoted to radiobiology (7–9).

Various physiological effects may be observed, depending upon the dose and type of radiation, as well as upon the type and strain of animal used. In theory, the appearance of any observable symptom of radiation may be used as the basis of a testing procedure, but in practice lethality has generally been the criterion for protection. Death may result from damage to the central nervous system, intestines, or the blood-forming organs, or with lower doses of radiation, through an increase in neoplasia. Enough animals need to be employed for statistical significance, and generally a 30-day period for survival is observed. Testing results are expressed most commonly as the percentage survival for the observation period in comparison to the survival of control animals. Another method of expression of test data is in terms of the dose reduction factor (DRF) (the ratio of the X-ray dose causing an LD_{50} in the treated animals compared to the X-ray LD_{50} in the unprotected animals).

The dose of protective agent used is generally as close to a toxic dose as possible. For this reason, therapeutic indexes are not expressed, since no definite effective dose is usually established. Deaths due to drug rather than radiation can be recognized by the time of death in comparison to that of the controls. Since the combined burden of compound toxicity and radiation damage may cause death with the treated animals but not with the controls, more than one dose level of protective agent should be employed. Radiation dosage is usually in the range of 700–1000 r, which is an amount sufficient to cause intestinal death. Rate of administration varies. Most antiradiation testing has been done against a single lethal dose of radiation, with a 30-day survival period, so information regarding protection against chronic or repeated radiation, or concerning long-term radiation effects has not been obtained for the majority of compounds tested.

Other testing procedures used to a much lesser extent include the inhibition of bacterial or plant growth, and the prevention of depolymerization of polymethacrylate or polystyrene (10) or of DNA (11). Plaque-forming ability of coliphage T (12), effect on Eh potential (13), inhibition of peroxide formation of unsaturated lipids or β-carotene (13), and inhibition of chemiluminescence of γ-irradiated mouse tissue homogenates (14) have also been employed as test procedures. Protection of cells in tissue culture has also been used (15), as well as spleen colony counts (16). A review of the nonlethal test methods has appeared (17). Agreement between these methods and that of animal mortality frequently does not hold, even for compounds of the same class.

PROTECTIVE COMPOUNDS

The more extensively investigated compounds have been well discussed in recent books by Thomson (9), and Bacq (18), and in numerous reviews. A complete catalog of compounds tested for radiation protection up to 1963 has been compiled by Huber and Spode (19), and a handbook of radioprotective agents appeared in Russia in 1964 (20). Reviews on protective agents that have appeared since 1963 are included in "Annual Reports in Medicinal Chemistry" (21). Volume I of "Progress in Biochemical Pharmacology" (22) is wholly concerned with radioprotective drugs and radiation sensitizers, and a chapter in "Progress in Drug Research" (23) is devoted to this topic. An annual bibliography on antiradiation drugs starting in 1959 (24) is also available. A variety of reviews on more specialized topics related to radiation biochemistry with more or less emphasis on radiation protection has appeared (21). Recent summaries of the chemical and biological effects of radiation are available (25, 26).

In the following discussion of structure-activity relationships, results on radioprotection of mice exposed to a lethal dose of ionizing radiation are compared unless otherwise stated. It should be realized that testing of other systems may give results which differ wholly or to a partial extent. Relevant details concerning radiation dose, compound dose, or strain of test animal, variations of which can alter results, are not included in the discussion, but radiation dose is included in Table I for a selected list of compounds.

Thiols and Thiol Derivatives—2-Mercaptoethylamine (MEA) and 2-mercaptoethylguanidine (MEG) (27), and derivatives of these structures, have constituted the most effective class of radiation-protective compounds. Since the initial discoveries of the protective action in mice of cysteine (4) by Patt and MEA (6) by Bacq, hundreds of derivatives and analogs of the mercaptoalkylamine structure have been synthesized and screened for radioprotective activity. Several structural requirements for activity in this class have become apparent.

1. The presence of a basic function (amino or guanidino group) located two or three carbon atoms distant from the thiol group appears to be essential. Activity declines abruptly with more than a three-carbon distance.

2. The thiol group should be free or readily converted to a free thiol *in vivo* for high activity. Several acyl thiol derivatives (I), including the thiosulfuric acid (28),

Table I—Radiation-Protective Compounds in Mammals

Compd.	Animal	Radiation Dose, r[a]	Protective Effect[b]	References
Derivatives of Cysteine and Cysteamine				
Alkyl and Aryl Derivatives				
Cysteine	Mice	800	3	4
Cysteamine (MEA)	Mice	700	3	6
Cystine	Mice	800	0	4
Cystamine	Mice	700	3	6
N-Methylcysteamine	Mice	500	2	88
N,N-Dimethylcysteamine	Mice	500	1	88
N,N-Diethylcysteamine	Mice	500	2	88
N-Piperidylcysteamine	Mice	500	0	88
N-Phenylcysteamine	Rats	500	0	88
Cysteamine-*N*-acetic acid	Mice	600	2	101
N-β-Phenethylcysteamine	Mice	1000 (γ)	3	32
3-Mercaptopropylamine	Mice	800	3	361
4-Mercaptobutylamine	Mice	800	1	361
2-Amino-1-pentanethiol	Mice	800	3	362
1-Amino-2-propanethiol	Mice	800	3	111
Homocysteine	Mice	700	2	87
S-Methylcysteamine	Mice	700	0	87
S-Benzylcysteamine	Mice	800	1	40
2-Mercaptoethylaminopropanesulfonic acid	Mice	800	3	42
L-3-Amino-4-mercapto-1-butanol	Mice	800	3	43
Methionine	Mice	500	0	98
Acyl Derivatives				
N-Acetylcysteamine	Mice	800	1	27
S-Acetylcysteamine	Mice	800	3	47
S-Benzoylcysteamine	Mice	800	1	47
Homocysteine thiolactone	Mice	550	2	363
Glutathione	Mice	950	2	96
N-β-Alanylcysteamine	Mice	500	1	98
N-Pantothenylcysteamine	Mice	500	0	98
S-2-Aminoethylthiosulfuric acid	Mice	1000	2	28
S-(2-Aminoethyl)-phosphorothioate	Mice	1092	3	29
S-(2,2-Dimethyl-2-aminoethyl)-phosphorothioate	Mice	1000 (γ)	3	37
2-Aminoethyltrithiocarbonate	Mice	800	3	364
S-L-Leucylcysteamine	Mice	825	3	100
N-Glutamylcysteamine	Mice	600	2	101
Other Basic Functions				
S-2-Aminoethylisothiuronium Br	Mice	800	3	27
S-3-Aminopropylisothiuronium Br	Mice	800	3	27
2-Guanidinoethyltrithiocarbonate	Mice	800	3	30
S-2-Guanidinoethylphosphorothioate	Mice	1092	3	44
N,S-Dioctanoyl-2-guanidinoethanethiol	Mice	800	2	30
2-β-Aminoethylmercaptoimidazoline	Mice	730	1	145
1,2-Dihydro-1-methyl-2-pyridinylimmonium 1,2-dihydro-1-methyl-2-pyridinyldithiocarbamate	Mice	800	3	54
N-Ethyl-α-acetamidinium thiosulfate	Mice	1000 (γ)	3	50
N,N'-Bis(mercaptoacetyl)hydrazine	Mice	800	3	56
Oxidized Derivatives				
2-Aminoethyl 2-aminoethanethiolsulfonate	Mice	800	3	67
2-Guanidinoethyl 2-guanidinoethanethiolsulfinate	Mice	800	2	68
2-Guanidinoethyl 2-guanidinoethanethiolsulfonate	Mice	800	2	67
o-(2-Aminoethyldithio)benzenesulfonic-acid	Mice	800	3	62
o-(2-Pyridylmethyldithio)benzoic acid	Mice	800	3	62
n-Decylaminoethyl-*N'*-acetylaminopropyl disulfide	Mice	825	3	63
Other Sulfur-Containing Compounds				
Ammonium dithiocarbamate	Mice	675–1200	3	70
Diethyldithiocarbamate	Mice	675–1200	3	70
2-Methylpiperazinedithioformate	Mice	1000	2	71
2-Piperazinoethyldithiocarbamic acid	Mice	600	2	72
Ethyl 9-acridyldithiocarbamate	Mice	1000 (γ)	2	55
Ethlene-bis-(*N,N'*-dimethyldithiocarbamate)	Mice	675–1200	2	70
2-Dithiocarbamoyl-3-dithiocarbonylthiopropanoate	Mice	800	3	74
N-(Dithioacetic acid *p*-nitrobenzylester)-pyridinium chloride	Mice	825	2	95
Tetrahydro-1*H*,3*H*-thiazolo[4,3-*c*][1,4]-thiazine-3-thione	Mice	100 (γ)	3	37
Thiourea	Mice	600	1	5
Dithiouracil	Mice	800	1	80
Dithiooxamide	Mice	800	0	80
N,N'-Dimethyldithiooxamide	Mice	800	2	80
2-Aminothiazoline	Mice	800	1	81
2-Mercaptothiazoline	Mice	800	2	40
3-Mercapto-*s*-triazole	Mice	900	2	139
2-Benzothiazolethiol	Mice	800	1	80
2,3-Dimercaptopropane-1-sulfonic acid	Mice	800	2	85
Pantoyltaurine	Mice	700	1	99
Dimethyl sulfoxide	Mice	1100 (rad)	3	89

(*Continued on next page*)

Table I—(*Continued*)

Compd.	Animal	Radiation Dose, r[a]	Protective Effect[b]	References
Nitriles				
Malononitrile	Mice	800	2	80
Hydroxyacetonitrile	Mice	800	3	80
2-Cyano-3,3-acrylonitriledithiol, diK salt	Mice	825	2	94
2-Cyano-3,3-acrylonitriledithiol, Zn salt	Mice	1000 (γ)	1	94
Compounds with Pharmacological Activity				
Histamine	Mice	700	3	99
Tryptamine	Mice	700	3	99
Serotonin-creatinine sulfate	Rats	880	3	147
3,4-Dihydroxyphenylalanine (DOPA)	Mice	700	2	99
Tryamine	Mice	700	2	99
Epinephrine	Rats	880	1	163
Vasopressin (Pitressin)	Rats	880	2	163
Reserpine	Mice	955	1	156
1-Hydrazinophthalazine	Mice	800	2	155
Guanethidine	Mice	800	2	155
Imipramine	Mice	800	2	158
p-Aminopropiophenone	Rats	880	3	147
Procaine	Mice	1025 (γ)	3	191
Other Compounds				
Benzimidazole	Mice	800	2	136
Quinoxaline-1,4-di-*N*-oxide	Mice	550	3	141
N-Phenyl-2-thiophenecarboxamidine	Rats	700	2	53
1-Phenyl-4,4-dimethylimidazolidine	Mice	800	1	80
Glycerol	Mice	700	2	116
Salicylic acid	Mice	700	2	87
Pyromellitic acid	Mice	1025	3	134
Propyl gallate	Rats	750	3	132
4-Hydroxybutyric acid	Mice	850	2	194
Ethylenediaminetetraacetic acid	Mice	700	2	116

[a]Refers to X-rays, unless otherwise indicated. [b]The grading of the optimal protective effect was done as follows: 3, strong protection; 2, moderate protection; 1, slight protection; 0, no protection.

phosphorothioic acid (29), and trithiocarbonic acid (30), most likely liberate free thiol in the animal; at least an increase in tissue nonprotein thiol levels has been reported for administration of the thiosulfate and phosphorothioate of MEA (31).

3. Alkylation of the nitrogen often results in some loss of activity. The *N*-β-phenethyl and *N*-β-thienylethyl derivatives of MEA, however, have good activity (32). The *N,N*-diethyl derivative also retains much of the activity of MEA; the *N,N*-dimethyl derivative is more toxic (33). The *N,N*-dipropyl and -diisobutyl derivatives retain a little activity, whereas the di-*n*-butyl derivative is inactive (33); other *N*-alkyl derivatives are listed in *Reference 23*. *N,N'*-Polymethylene bridging of the MEA structure provided compounds, $XS(CH_2)_2NH(CH_2)_n$-$NH(CH_2)_2SX$, which were active where X was PO_3H^- and *n* was 3 or 4, but inactive where X was SO_3H (34).

4. Alkylation of the carbon atoms has given varied results. Active compounds have been found among C-monoalkyl derivatives of MEA, 2-aminopropane-1-thiol and 1-aminopropane-2-thiol being strongly protective (35). Whereas α,α-dialkyl-β-aminothiols are inactive (36), some β,β-dialkyl-β-aminoethane thiosulfates and phosphorothioates (II) however, have protective activity (37). 2-Amino-1-pentanethiol and 2-amino-3-methyl-1-butanethiol also had good activity (37). The presence of phenyl groups has been claimed to give active compounds when located β to the amino function (38); others have found phenyl groups to block activity (39).

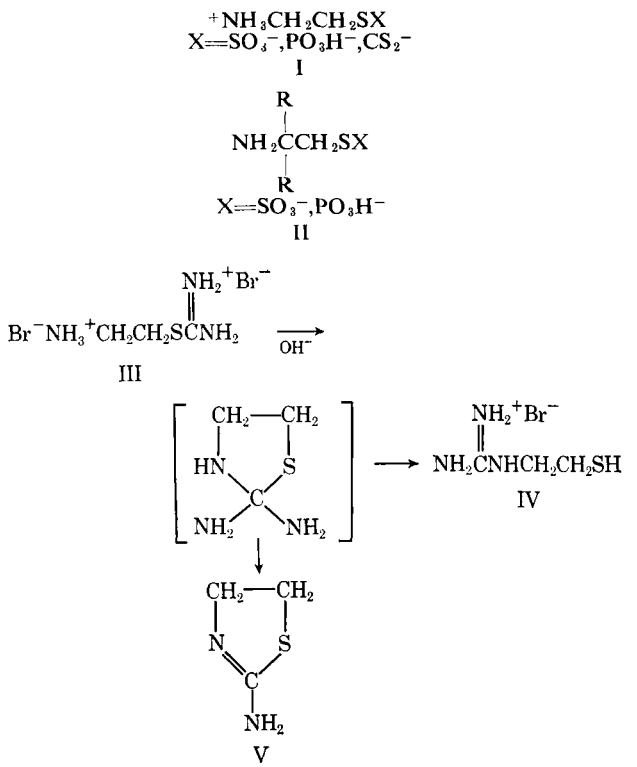
5. Alkylation of the sulfur generally results in loss of activity. The *S*-benzyl derivative of MEA has some activity, however (40).

Other functional groups in the MEA structure have usually caused diminution or loss of activity. Presence of a carboxyl group frequently gives less activity; cysteine has the same dose reduction factor in mice (1.7) as MEA or MEG, but a much larger dose is required (41). Protective activities for cysteine, homocysteine, and their derivatives have been adequately discussed by Melching and Streffer (23). *N*-Monosubstituted derivatives containing thioureido or sulfone substituents were found inactive, although sulfonic acid zwitterions, $HS(CH_2)_2NH_2^+(CH_2)_3SO_3^-$, were protective (42). The presence of hydroxyl appears to favor activity, *e.g.*, L(+)-3- amino-4-mercapto-1-butanol gave good protection to mice (43) (*cf.* 45). An additional thiol group diminishes activity; several 2-alkyl-2-amino-1, 3-propanedithiols showed little protection in mice (43).

S-Acylation of the MEA molecule has provided some very active compounds, particularly where zwitterions have resulted. The thiosulfate, or Bunte salt (28), phosphorothioate (29), and trithiocarbonate (30) of MEA, all of which form zwitterions, have protective activities comparable to that of MEA. Corresponding zwitterions of MEG are also equal in activity to MEG (30, 44). Of these *S*-acyl derivatives, the phosphorothioates have been particularly effective; *S*-(3-amino-2-hydroxypropyl)-phosphorothioate and *S*-(2-amino-

propyl)-phosphorothioate have DRF values in mice of 2.16 and 1.86, respectively, in comparison to a DRF value of 1.84 for MEA (45). The inorganic relatives, diammonium amidophosphorothioate and thioamidodiphosphate, surprisingly gave DRF values, respectively, of 2.30 and 2.16 at relatively low doses (45). It is believed that the phosphorothioate group aids in cellular transport (46). Sulfonate zwitterions containing dithiocarbonate group, $^{+}NH_3(CH_2)_2SCOS(CH_2)_nSO_3^{-}$, however, were inactive (42). In a series of straight-chain aliphatic thioesters of MEA, the best protection was found with the acetyl and octanoyl derivatives (47); the benzoyl ester had but slight activity. The Bunte salts of MEA and derivatives are claimed to have about one-half the toxicity of the parent mercaptans (48).

Other basic functional groups can replace the amino group in the MEA structure to give radioprotective thiols. Replacement by the guanidino group has resulted in two very active compounds, 2-mercaptoethylguanidine (IV) (MEG) and 2-mercaptopropylguanidine (MPG) (27). Solutions of these compounds were obtained through the aminoalkylisothiuronium salts by alkaline rearrangement. When these compounds are employed for radiation protection, the hydrobromides of 2-aminoethylisothiuronium bromide (AET) (III) or 3-aminopropylisothiuronium bromide (APT) are dissolved in neutral or alkaline media, which gives immediate rearrangement to MEG or MPG (Scheme I). These compounds may be isolated as the sulfates (49) or trithiocarbonate esters (30). With more than three carbon atoms between the amino and isothiuronium functions, rearrangement does not readily occur and the isothiuronium salts give little protection.



Scheme I—Transguanylation of AET [*Khym* et al. (*82*)].

Replacement of the amino group by amidino has also given compounds with good protective activity, particularly with the Bunte salts of α-mercaptoacetamidines (50) (VI). Other amidines related to MEA and MEG have been effective; 3,3′-dithiobis-(propionamidine) (51) and propionamidines containing isothiuronium groups (52), for instance, have shown good activity. *N*-Phenyl-2-thiophenecarboxamidine and the corresponding furan derivative (53) are also radioprotective in rats.

Use of strongly basic nitrogen heterocycles having pKa values of 10–12.5 has also provided protective compounds having the dithiocarbamate group as the sulfur-containing function (VII). Reaction of imino-*N*-alkylpyridines (54) and acridines (55) with carbon disulfide gave imino-*N*-carbodithioates having moderate protective effects.

Substitution of the hydrazino group for amino has not provided many active compounds. Protection of mice has been reported for *N,N′*-bis-(mercaptoacetyl)-hydrazine (56), however, as well as for *N*-acetylthioglycolic hydrazide, $HSCH_2CONHNHCOCH_3$ and its disulfide (57).

Oxidation of the thiol group of the MEA structure has given products with some radiation-protective properties, but in each active case liberation of the MEA or *N*-substituted MEA thiol anion is still possible. The disulfides of MEA (cystamine) and MEG (GED) are as active as the parent thiols; GED is more toxic than MEG, and consequently has a lower DRF (58). It is not yet known whether the thiol or disulfide is the active form of these compounds; evidence exists for both possibilities. In the case of GED, appreciable amounts of this disulfide are found *in vivo* after administration of either MEG or GED (59). Some *in vitro* systems protected by MEA are not protected by cystamine, however (60).

Cystine is nonprotective in mammals, probably because of its inability to penetrate some cellular membranes (61). Mixed disulfides of MEA have provided good protection, particularly those derived from *o*-substituted mercaptobenzenes where zwitterions are formed with carboxyl or sulfonyl anions (62) (VIII). Mixed disulfides containing *N*-decyl MEA are also effective (63); as is the mixed disulfide of thiolacetic acid and *N*-acetyl MEA (64). Other disulfides, lacking basic groups, have generally been found inactive.

Higher oxidation states of the sulfur in the MEA and MEG molecules have been obtained, and some protective activity found. The thiolsulfinates of both MEA (65) (IX) and MEG (66) have been prepared, as well as the corresponding thiolsulfonates (67) (X). Protective activity has been reported for both of the thiolsulfonates (67) and the thiolsulfinate of MEG (68); the thiolsulfonates of MEA as well as of its *N*-acyl and *N*-decyl derivatives had greater activity than the thiolsulfonate or thiolsulfinate of MEG. Thiolsulfinates and thiolsulfonates may also be considered acylation products of the thiols by sulfenic and sulfinic acids. Taurine and hypotaurine (the SO_3H and SO_2H derivatives, respectively, of MEA), both metabolites of MEA in mice (69), provide very little protection (18).

Other Sulfur-Containing Compounds—A number of dithiocarbamates have been found with good protective effects. The radiation dosage level for which these compounds provide appreciable protection has frequently been lower than that at which the amino thiols are effective, but this may be partly due to differences in laboratory procedures. The simplest compounds of this type, either with the nitrogen unsubstituted or bearing small alkyl groups, up to *n*-butyl, have shown the most activity (70). The *N,N*-dialkyl derivatives, however, are more effective than the mono-*N*-alkyl compounds; 2-methylpiperazinedithioformate (XI), for instance, gives protection against a high dose of X-irradiation (1000 r) (71). The mechanism by which the dithiocarbamates protect is believed to differ from that of the amino thiols. Dithiocarbamates are known as powerful metal-binding agents, but the inclusion of an additional metal-binding group (hydroxyl or amino) in dithiocarbamate molecules did not increase protective ability (72). A cyclic dithiocarbamate, tetrahydro-1*H*, 3*H*-thiazolo-[4,3-*c*]-1,4-thiazine-3-thione (XII), has been reported with good activity (35). Xanthates have not been found protective (73).

Reaction of cysteine with carbon disulfide gave the trithiocarbonate dithiocarbamate (74) (XIII), which possessed activity equivalent to that of MEG but which was only about one-third as toxic. A metabolism study in mice showed the dithiocarbamate group to be stable *in vivo* but the trithiocarbonate to be unstable (75); the dithiocarbamate is most likely the active form. An attempt to prepare *S*-mercaptoethyldithiocarbamates gave only the dithiocarbamate disulfides, which proved to be inactive (76).

Thioureas and cyclic thioureas have shown only marginal or no protection. Thiourea itself protects mice only in massive doses (2,500 mg./kg.) (5). Thiouracil is not protective, but dithiouracil affords some protection (77). Dithiooxamide likewise is nonprotective, but some *N,N'*-dialkyldithiooxamides provide significant protection (77). *S*-Alkylisothioureas, with alkyls up to *n*-butyl, have shown moderate protective effects (78). Guanylthiourea *p*-toluenesulfonate was claimed to protect mice *versus* 900 r (79); the orthophosphate of this compound (thiocarbamylguanidinium orthophosphate) was inactive in mice *versus* 800 r (80), however.

A number of thiazoles, thiazolines, and thiazolidines have been examined for radiation protection; probably the most effective compound of this class is 2-aminothiazoline (81) (V). This compound is derived from AET at pH 2.5, and is converted to an open-chain compound, possibly *N*-carbamylcysteamine, at pH 9.5 (82). 2-Mercaptothiazoline has been found to be active in two laboratories (8, 40), others have found it inactive (77, 81). 2-Mercaptobenzothiazole (8, 77) and 2-mercaptobenzoxazole (77) are both protective, but the nitrogen analog, 2-mercaptobenzimidazole, is not (77). Several thiazolidines have provided protection, which was attributed to ring opening to give mercaptoamines (83).

Simple, nonbasic thiols have not been found effective as radiation protectors. Conflicting reports have been made for the dithiol BAL as well as for thioctic acid (18). Other dithiols have been inactive with the exception of 2,3-dithiosuccinic acid, which was protective in mice *versus* 700 r (84). A derivative of BAL, 2,3-dimercaptopropanesulfonic acid (Unithiol) is moderately active (85). β-Mercaptoethanol protects bacteria (86) but not mice (87); it has also been found to be radiosensitizing (88).

Other sulfur-containing compounds with significant protective ability include dimethyl sulfoxide when given in large doses (89) (other sulfoxides have shown little or no protection). Organic thiosulfates, other than those that liberate MEA or an active derivative of MEA, have usually been inactive. Moderate protection was found for the thiosulfate of an amide of β-mercaptopropionic acid, however (46). Inorganic thiosulfate is a good protector of macromolecules *in vitro* or of the mucopolysaccharides of connective tissues *in vivo* (90); it does not protect animal cells, however, because of its inability to penetrate. The antibacterial sulfonamides have afforded some protection, sulfamethazine being the most effective (91).

Mercapto acids have shown little protection, with the exception of thioglycolic acid, which may be slightly protective, inactive, or sensitizing, depending on the system tested (18). The β-aminoethylamide of thioglycolic acid, $HSCH_2CONHCH_2CH_2NH_2$, has good activity (56), however. α-Thiopropionic acid had a small protective effect in rats, whereas β-thiopropionic acid was inactive (92). In a series of cysteine ester hydrochlorides, the propyl ester was the most effective (92); these esters differed biochemically from cysteine.

Thioacids and their derivatives have generally been inactive, although α-aminothiopropionic acid has slight activity in mice (93). Others have claimed that the thioacids derived from glycine and α- and β-alanine were inactive in rodents (56). Dithio acid dianions (XIV), obtained by condensation of carbon disulfide with nitriles, *e.g.*, 2-cyano-3,3-dimercaptoacrylonitrile and 2-benzoyl-3,3-dimercaptoacrylonitrile, have been found protective (94). Dithio esters obtained from pyridinium dithioacetic acid betaine have also shown protective ability (95) (XV).

Naturally occurring thiols have not been appreciably protective in animals with the exception of glutathione (96), which is moderately active. Ergothioneine (the betaine of thiolhistidine) (97), pantetheine (*N*-pantothenylcysteamine) (98), and aletheine (*N*-β-alanylcysteamine) (98) have been found inactive. Pantoyltaurine (99) apparently has some activity. Bacq (18) has presented arguments which make it appear unlikely that coenzyme A is involved in radioprotection. Both *S*- (100) and *N*-acylation (101) of MEA with α-amino acids, however, have provided active compounds. *N*-Glutamylcysteamine as well as *N*-gluconylcysteamine and cysteamine-*N*-acetic acid (*N*-2-mercaptoethylglycine) (101) were found effective.

Incorporation of thiol and either amino (102) or guanidino groups (103) on adjacent carbons of monosaccharide molecules has been accomplished, but no testing data were reported for these compounds. The inclusion of mercaptoethylamine moieties in sugar molecules has also been done (104). Stereochemical arrangements have been determined for some of the aminomercaptosugars, so testing data here would

indicate whether stereochemistry is important in radiation protection. The D and L isomers of 2-aminobutylisothiuronium bromide, a particularly effective derivative of AET, have been separated, however, and the D isomer was twice as active in mice *versus* 900 r as the L isomer (105). A small difference in activity was also found for the *cis* and *trans* isomers of 2-aminocyclohexan-1-thiol (105*a*).

Cyanide, Nitriles, and Other Metabolic Inhibitors—Cyanide ion has been found radioprotective in a number of laboratories (3, 106, 107), but it must be administered immediately before irradiation because of its rapid detoxication (9). It has a number of biological properties in common with thiols, such as reduction of disulfide linkages and inhibition of copper-containing enzymes, but unlike the thiols it also inactivates cytochrome C oxidase, which controls oxygen consumption in mammals. Other enzyme inhibitors have been radioprotective; azide (108), hydroxylamine (109), and 3-amino-1,2,4-triazole (110) are weak protectors. The latter two compounds are inhibitors of catalase, but no relation between their effect on catalase and radioprotection was apparent.

Several organic nitriles have shown radioprotective effects, which have been attributed to liberation of cyanide ion *in vivo*. These include malononitrile (108), hydroxyacetonitrile (77), and 2-hydroxybutyronitrile (111). Hydroxyacetonitrile is comparable to the aminothiols in protective ability. Moderate protection was provided by the dimercaptoacrylonitriles (94) previously mentioned, and weak protection was found with an α-alkyloxyiminonitrile (112).

Fluoroacetate is protective (113) when sufficient time is allowed before irradiation for its conversion to fluorocitrate, an inhibitor of citrate metabolism. Other thiol group or enzyme-inhibiting agents, such as iodoacetic acid, malonic acid, mercurials, and arsenicals have no protective ability, but many of these agents have shown radiosensitizing effects.

Metal-Binding Agents—A number of metal-binding agents are radioprotective and are also known to inhibit enzymes. Some metal complexes imitate the action of enzymes, such as copper complexes which catalyze the decomposition of peroxides (114). These effects may play some role in radiation protection. Metal-binding agents already discussed include the dithiocarbamates as well as the aminothiols (115). EDTA in very large doses protects mice (116); this is probably necessary because little EDTA enters the cells. Oxine (8-hydroxyquinoline) is too toxic for animal studies, but was found highly protective in a polymer system (87). Other common metal-binding agents, such as *N*-nitroso-*N*-phenylhydroxylamine and nitrilotriacetate have shown appreciable protection (117), as has 3,5,6,-trihydroxy-*N*-methylindole (116). Derivatives of 1,5-diphenylthiocarbohydrazide, avid metal binders, have protected mice, rats, and dogs (118).

Some metal complexes have been tested and found protective. Iron complexes of polyamines (119) are active, as well as zinc complexes of MEA and MEG, the copper and iron complexes showing little or no activity (115). Copper complexes of diethyldithiocarbamate, dithiooxamide, and oxine were also found to give less protection than the uncomplexed agents themselves (87). Complexes of chlorophyllin (with Co, Mg, Mn, V) are radioprotective in mice (120).

Amines and Amino Acids—Few protective compounds have been found in this class of compounds, with the notable exception of cysteine (4). Glycine has a little activity in mice (121) but is appreciably protective for some enzymes (122). α-Alanine has been claimed to be both a radiosensitizer (123) and protector (99) in mice. Similar claims have been made for methylamine (99, 123); no effect was found by another investigator (124). Ethylamine is inactive, but a moderate effect is shown by ethanolamine (99, 123, 124), as well as by dimethylamine and trimethylamine (99). Several diamines are active, including propylenediamine and 1-guanidino-5-aminopentane, the decarboxylation product of arginine (99).

Hydroxyl-Containing Compounds—Ethanol in large doses protects mice (125). Glycerol is protective in mice as well as in other systems (5, 116, 126); propylene glycol also has a moderate effect in mice (87). Other alcohols and glycols have not been appreciably protective. In tests with *E. coli*, DRF values for glycerol, ethylene glycol, and methanol were 3.71, 2.03, and 1.42, respectively (127). Mono- and disaccharides show only weak effects, the best probably shown by fructose (87). In a series of 15 polyhydroxy alcohols derived from sugars, only ribitol gave a retardation in mortality of mice (128). Inositol protects when given in large doses (129).

Phenols are protective in polymethacrylate tests (87), but many of them are too toxic for animal tests. The catecholamines have provided protection, possibly by lowering oxygen tension in the cells (18). An auxin analog, β-2,4,5-trichlorophenoxyethanol (130), and 2,4-dinitrophenol (131) may act in the same fashion, since they increase oxygen consumption. The protective effects of gallic acid esters are attributed to inhibition of chain oxidation processes induced by radiation (132). Arachidoyl derivatives of pyrogallol and the naphthols have shown activity (133).

Organic acids, including pyruvic, formic, and caprylic (87) provide only weak protection; acetic acid is ineffective. The polycarboxylic acids, pyromellitic and benzenepentacarboxylic, but not mellitic acid, gave good protection to mice *versus* 1025 r (134). These polyionic substances were believed to protect by causing hypoxia from osmotic effects, rather than by chelating calcium ion, which also has an effect on radiation damage. Calcium salts of acids, such as acetate and lactate, also have a small protective effect (135) in rats.

Heterocyclic Compounds—Several relatively simple heterocyclic compounds have provided good protective activity. In a series of imidazoles, imidazole itself, benzimidazole, and 1-naphthylmethylimidazole were the most effective compounds (136). Related heterocycles with protective activity include 1-phenyl-4, 4-dimethylimidazolidine (80), a sugar derivative of imidazoline-2-thione (137), and 3,5-dimethyl-1-(dimethylcarbamoyl)-pyrazole (138). Carbazole (80) also gives slight protection.

A series of *s*-triazoles, mesoionic *s*-triazoles, and fused-ring triazoles revealed little activity, with the exception of triazole-3-thiol (139). Slight activity was provided by *s*-triazolo[4,3-α]pyridine-3-thiol and anhydro-2,4-dimethyl-5-hydroxy-3-phenyl-*s*-triazolium hydroxide. The presence of strongly nucleophilic sulfur in these compounds did not confer appreciable protective activity.

Of a large number of amine oxides tested for radiation protection (140), quinoxaline-1,4-di-*N*-oxide (XVI) (believed to act in part by radical trapping) was the most effective. It is protective in mice but radiation-sensitizing in the dog (141). 2*H*-1,3-Benzoxazine-2,4-dione was found as effective in mice as cysteine (142), and 3,5-diamino-1,2,4-thiadiazole (79) and 3-(β-aminoethyl)-1,3-thiazane-2,4-dione have some protective activity (143). Aminoethyl and aminomethyl purines and pyrimidines gave one-third as much protection in mice as MEA (144). The cyclic analogs of AET, 2-aminoethyl- and 2-aminopropylthioimidazoline, are moderately protective; the corresponding tetrahydropyrimidines had little activity (145). A synthetic polymer prepared from *N*-vinylpyrrolidone and *S*-vinyl-(2,2-dimethylthiazolidyl)-*N*-monothiolcarbamate was protective, possibly by liberation of thiol groups on hydrolysis *in vivo* (146).

Pharmacologically and Physiologically Active Substances—A number of commonly used pharmacologic and physiologic agents provide radiation protection which is generally of lower order of activity than that provided by the amino thiols. A notable exception is 5-hydroxytryptamine, which is equal in activity to that of the most effective thiols (99, 147). Many of these agents are believed to be radioprotective by virtue of their ability to lower oxygen tension in the cells.

Central nervous system drugs have only small or moderate effects as radiation protectors. Pentobarbital has a slight effect in guinea pigs (148), and nitrous oxide is effective in the presence of oxygen, both in mice (149) and Ehrlich carcinoma cells (150). Morphine, nalorphine, and codeine (151) as well as heroin (152) give moderate protection. Salicylic acid also has a moderate effect (87). Reserpine is effective when given 12–24 hr. before irradiation (153), possibly by release of serotonin and catecholamines (154). Two other hypotensive agents, 1-hydrazinophthalazine and guanethidine (155) have some protective effect. Chlorpromazine exerts a slight effect when given 4.5 hr. prior to irradiation, when a state of hypothermia exists (156), or when the body temperature of the animals is reduced to 31° (157). Other psychotropic drugs reported to be effective protectors include imipramine (158) and chlorprothixene[1] [2-chloro-9-(3-dimethylaminopropylidene) thioxanthene] (159). The latter drug was most effective when body temperature and metabolism were depressed.

Central nervous system stimulants have generally been nonprotective. An exception is found in the magnesium complex of pemoline (2-imino-5-phenyl-4-oxazolidinone) which gave moderate protection to mice *versus* 750 r (160). Dextroamphetamine was inactive under these conditions. Complamine, a derivative of caffeine and nicotinic acid, is also protective (161).

The different classes of autonomic drugs provide some radiation protection; the causative factor is believed to be production of hypoxia by various mechanisms, such as through vasodilatation or reduction of blood flow in the viscera. Acetylcholine (124) and other choline esters (162), epinephrine (163), phenylephrine (164), tyramine (87), *m*-hydroxyphenylalanine (8), β-phenethylamine (8), methoxamine (165), dopamine (166), isopropylarterenol (167), and *N*-methyl-1-phenyl-2-propylamine (156) have all been described as conferring some protection to mice or rats. The cholinomimetic compounds arecoline, tremorine, and oxytremorine (168) also provided good protection to mice. Norepinephrine, which decreases oxygen tension in the spleen much less than does epinephrine, gave very little protection to mice (169). *N*-Substituted derivatives of MEA containing such substituents as norephedrine, amphetamine, norepinephrine, *o*-alkoxyphenoxyalkylamines, and 2-phenylcyclopropylamine to aid in transport of the MEA function failed to show significant protection (170).

A state of anoxia may also be produced by methemoglobin formation, which has been considered to be the means by which *p*-aminopropiophenone (PAPP) is radiation protective (171). Other compounds which alter the ability of hemoglobin to transport oxygen, and which have shown some radioprotection include sodium nitrite (172), aniline (87), aniline derivatives (173), and carbon monoxide (174). No correlation between methemoglobin formation and radiation protection has been found (175), although the protection afforded by PAPP is removed by increased oxygen pressure during irradiation (176). More recent findings show the protective effect of PAPP to be independent of the degree of methemoglobinemia (177).

5-Hydroxytryptamine (serotonin) has already been mentioned as equal in protective effects to the amino thiols; it is effective however, at a dose well below the toxic level (77), unlike the thiols. A DRF value of 1.85 has been reported (178). Its activity has been attributed to its vasoconstrictor effect causing hypoxia of radiosensitive tissues (146); some support for this is found in the removal of its protective action by pharmacologic antagonists (179). 5-Hydroxytryptophan is comparable in activity to serotonin (180). The 5-methoxy ether is also a good protector, but higher alkyl ethers did not affect survival (181). Other derivatives are considered in *Reference 23*. Irregular results have been reported for histamine (87, 123, 182); it is most likely effective through tissue hypoxia as a result of decreased blood pressure (183). The polypeptides vasopressin[2] (163) and oxytocin (184) may also protect by producing a hypoxic state in some tissues.

Physiologic changes can probably account for the radioprotective action of some substances. Urethan (185), estrogens (186), and colchicine (187) can stimulate blood cell production by damaging bone marrow.

[1] Taractan, Hoffmann-LaRoche Inc., Nutley, N. J.

[2] Pitressin, Parke-Davis, Detroit, Mich.

If irradiation is carried out with an increased leucocyte/lymphocyte ratio in the blood, a greater percentage of more radio-resistant cells are present, and may enhance survival. Colchicine may also be effective by inhibition of mitosis, which could also result in the presence of more radioresistant cells, but there is evidence against this supposition. Colchicine is protective only when administered 2 or 3 days prior to irradiation, by which time mitotic inhibition has ceased. Urethan and the estrogens are similar in that they must be administered a day or more before irradiation. The proestrogen, tri-*p*-anisylchloroethylene, is effective when given 5–30 days before irradiation (188). Other inhibitors of mitosis however, can enhance protection; these include demecolcine (Colcemide), sodium arsenite, epinephrine, cortisone, and typhoid-paratyphoid vaccine (189).

Bacterial endotoxins have shown good radioprotective properties in both normal (187) and germ-free mice (190), probably by decreasing blood flow in capillaries and causing tissue hypoxia (190). Fluoroacetate exerts a moderate protection probably by causing an accumulation of citrate; radioprotection is coincident with a high tissue concentration of citrate (113). Citrate given directly is not radioprotective, probably due to poor penetration of cellular membranes.

Procaine (191) and several of its derivatives, particularly *p*-nitro procainamides (192), have good protective activity. In this connection, 1-phenyl-1-acetthio-2-nitroethane and its higher homolog were active in mice, while the corresponding amino compound, 1-phenyl-2-aminoethanethiol, was inactive (193). 4-Hydroxybutyric acid and 6-phosphonogluconolactone, substances which stimulate turnover of $NADP \cdot H_2$, a physiological reducing agent, provide protection to mice *versus* 900 r (194). An antihistamine, thenalidine, also affords moderate protection (191).

β-Melanocyte-stimulating hormone is radioprotective in both rats and mice (195), probably by stimulating release of catecholamines. Alloxan has protected both mice (196) and the pancreatic ultrastructure in dogs (197).

Metabolites and Naturally Occurring Compounds—A variety of compounds of these categories has been examined for radiation protection, but few really effective protective compounds have been found. Some polysaccharides, such as dextran (198), and mucopolysaccharides (199) (in local protection of the skin) have been protective. Polysaccharides extracted from typhoid and Proteus organisms (200), and a lipopolysaccharide from *S. abortus* were protective in mice, (201) possibly by inducing phagocytosis. Typhoid-paratyphoid vaccine (202) shows similar protection, which is enhanced by α-adrenergic blockade (203). Reference has already been made to the bacterial endotoxins (187, 190), which are lipopolysaccharides of molecular weight around 1,000,000.

Vitamins and coenzymes have not as a class been protective. Pyridoxal phosphate, however, has a moderate effect (204) which may be connected with a recovery rather than protective process (205). Several thiol-containing derivatives of vitamin B6, including 5-mercaptopyridoxine (206) and 4-deoxy-5-mercaptopyridoxine (207) were protective in mice; 3-mercaptomethylpyridine had no effect. Vitamin B12 and folic acid are protective in rats (208), and thiamine tetrahydrofurfuryl disulfide was effective in both mice and rats (209). Thiamine was much less effective. Calcium pantothenate has also been claimed to be radioprotective (210).

Some of the naturally occurring pyrimidine bases and nucleotides (211), including ATP (212), have an effect in mitigating radiation damage, but their value may be greater for postirradiation repair than for radioprotection. Protection from DNA, RNA, and derivatives has been claimed, and could be distinct from postirradiation repair (212–215). Uridine, but not cytidine, monophosphate is protective (216).

Among the commonly used antibiotics, the tetracyclines have shown the most favorable effects on survival rates in mice (217); this was believed due to increase in metabolic activity. Chloroquine diphosphate was also protective in mice *versus* 600 r (218), possibly by activation of the pentose cycle, or by binding to nucleic acid.

Other naturally occurring substances for which protective activity has been claimed include leucodelphinidine (219), tea catechols, and a gallate-tannin complex (220). The latter compounds probably act as antioxidants for radiation-induced oxidations. The radioprotective effects of rutin and other flavonoids have been controversial; 5,7-dihydroxyisoflavones were effective *versus* 700 r when administered to mice percutaneously but not intraperitoneally (221). Their favorable effect is presumably due to protection of the capillaries.

Other Compounds—Selenium analogs of AET, MEG, and 2-aminothiazoline have been prepared, but no antiradiation activities were reported (222). Selenomethionine and selenocystine have provided better protection than the analogous sulfur compounds for amino acids, yeast alcohol dehydrogenase, and RNase (223), however. Replacement of the thiol group of MEA with the phosphoric acid group, to give 2-aminoethylphosphoric acid, gave a protective compound (224). In a series of thiophosphate esters designed to form reversible complexes with cholinesterase, only two had appreciable radioprotective activity (225); no correlation with anticholinesterase activity was found. It should be added that the adenosine phosphates are protective (211*b*).

Inorganic phosphates have also been radioprotective. Reference has already been made to diammonium amidophosphorothioate and thioamidodiphosphate (45); octaethylpyrophosphoramide gave good protection to mice (226*a*) and trimetaphosphate (a cyclic compound) has a marked protective effect as well (226*b*). A comparison of the effect of various anions on radiosensitivity in mice showed the sulfide anion to be most protective (227). The slight protective effects of some calcium salts has been mentioned (135); parathormone, which increases calcium blood levels in mammals, also reduces radiation damage (228) either before or after irradiation. Cobalt salts have some activity in mice (229), and slight protective effects have been shown by magnesium salts (230).

RADIATION SENSITIZERS

An increase in the damaging effects of radiation may be caused by high doses of a compound, including good protectors, by addition of the toxicity of the compound to that of the radiation. Some compounds, however, appear to have a true sensitization effect, which is often difficult to distinguish from additive toxicity (9). Some of the sensitizations reported, however probably represent additive toxicities.

Several relatives of the cysteine structure have been recognized as sensitizers (88). These include isocysteine, β-homocysteine, and D-penicillamine; thioglycol and thioglycolic acid (231) have also caused sensitizations. Thiamine diphosphate (232), riboflavin (233), and menadiol sodium phosphate (Synkavit) (2-methyl-1,4-naphthohydroquinone diphosphate) (234) have acted as sensitizers in animals. Demecolcine sensitized mice when administered 12 hr. prior to irradiation, probably due to intestinal damage, but was radioprotective when given 48 hr. prior (235).

The common thiol-binding reagents have often produced sensitizations in animals. These have been observed for *p*-chloromercuribenzoate (236), iodoacetate (237), iodoacetamide (238), and *N*-ethylmaleimide (238) in mice. Sensitization of mice or rats has also occurred with pentobarbital (239), nalorphine (240), methyl ethyl ketone peroxide (241), hematoporphyrin (242), methylhydrazine (243), and cupric salts (244). Sensitization by cupric salts was prevented by thiols. Halogenated pyrimidines, particularly 5-bromo- and 5-fluorouracil (245) are consistent sensitizers. The halogenated thymidine analogs, 5-bromo- and 5-iodo-2-deoxyuridine also sensitize; these compounds evidently act by incorporation into DNA (246). Other halogen compounds, such as chloro- and fluoroacetic acids, chloroform, and trichloroacetic acid, as well as methanesulfonate, have sensitized rabbit erythrocytes (247). The role of halogenated thymidine analogs in inducing cellular radiosensitization has been reviewed (248).

A variety of compounds have also sensitized bacterial cells and enzymes to radiation. Thiol-binding reagents, stable free radicals, and halogen compounds, including the halogenated pyrimidines have caused sensitizations (243). Other bacterial sensitizers include hadacidin (249), chloral hydrate and other halides (250), quaternary heterocyclic salts, such as phthalanilides, phenaziniums, and isoindoliniums (251), methylhydrazine (243), methylglyoxal (252), 1-(β-D-arabinofuranosyl) cytosine (253), tetracyclines (254), triacetoneamine-*N*-oxide (255), and some irradiated cupric salts (256). Many of these compounds, including cupric salts, *N*-oxides, and nitroxide-free radicals (257) are more effective sensitizers under anoxic conditions.

RADIATION-PROTECTIVE AGENTS AND RADIOSENSITIZERS IN RADIOTHERAPY OF TUMORS

The use of radiation-protective or -sensitizing drugs to augment the effects of radiation of tumors has shown some success in animal experiments. For this type of therapy to succeed, a selective concentration of a protective drug in noncancerous tissue or of a sensitizer in cancerous tissue must be realized. Relatively few studies of such selective distributions between healthy and tumor tissue have been reported.

No distinct advantages have been reported in the use of a number of radiation protectors in connection with radiation of tumors, usually because of protection of the tumor tissue. This has generally been the result with MEA, cysteine, and serotonin (258) in tumor-bearing animals. Concentrations of AET in several types of tumors have been lower than in normal tissues (259, 260), however. Others found no protection given to a mouse tumor by MEA; but Crocker sarcoma was protected by MEA, menadiol, and nicotinamide, and not by serotonin or thiourea (261). Ehrlich ascites tumor was protected by 6-aminonicotinamide and menadiol diphosphate (261). Cysteine thiosulfate also protects Crocker sarcoma in mice (262). Heterologous RNA gave some protection to mice with Ehrlich ascites tumor but did not protect the tumor cells (263). Two antibiotics, but not streptomycin, protected four strains of ascites tumor cells (264).

A combination of AET, serotonin, cysteine, and glutathione was definitely favorable to the survival of mice with Landschutz ascites tumors treated with 6,000 r (265). Favorable effects on irradiation of mice with Ehrlich tumors were observed for AET and *dl-trans*-2-aminocyclohexanethiol, but were much less for menadione-$NaHSO_3$ and an oxindole derivative (266). Distributions of MEA released from the phosphorothioate and thiosulfate of MEA in various tissues have been found (267); the phosphorothioate of MEA showed a lower concentration in sarcoma M-1 than in the organs (268).

Results of a more promising nature have been obtained with the use of radiation sensitizers, and some clinical use has been reported. Thymidine analogs which modify the structure of DNA, such as 5-iodo-2′-deoxyuridine, have improved the effects of irradiation of tumors both in animals (269) and human patients (270). 5-Fluorouracil and 5-fluoro-2′-deoxyuridine have also been of value in advanced cancer cases (271). Actinomycin D also potentiates the therapeutic action of radiation, and has been used in radiation treatment of Wilms' tumor (272). This compound is known to complex with DNA, as does acriflavine, which has also been radiation sensitizing in tumor-bearing animals (273). The effect of cyclohexanol succinate has been controversial, although it is apparently effective in radiotherapy of squamous carcinoma of the skin (274). Menadiol sodium phosphate concentrates selectively in some animal and human tumors, and has given favorable results in carcinoma of the bronchus (275).

Other sensitizers which have shown favorable effects in radiation of animal tumors include methylethyl ketone peroxide (276), hematoporphyrin and its copper complex (277), 6-azauracil riboside (278), the pyrimidines pentoxyl and metacil (279), 6-methylthiouracil and thyroidin (280), menadione (281), and several dihydroxy and dicarboxy thiophenes and sulfides (282). Radiosensitization of HeLaS3 tumor cells *in vitro* by *N*-ethylmaleimide has been observed (283). 6-Chlorothymine also aids in reducing Ehrlich carcinoma growth in mice *versus* 2,500 r (284), and sodium per-

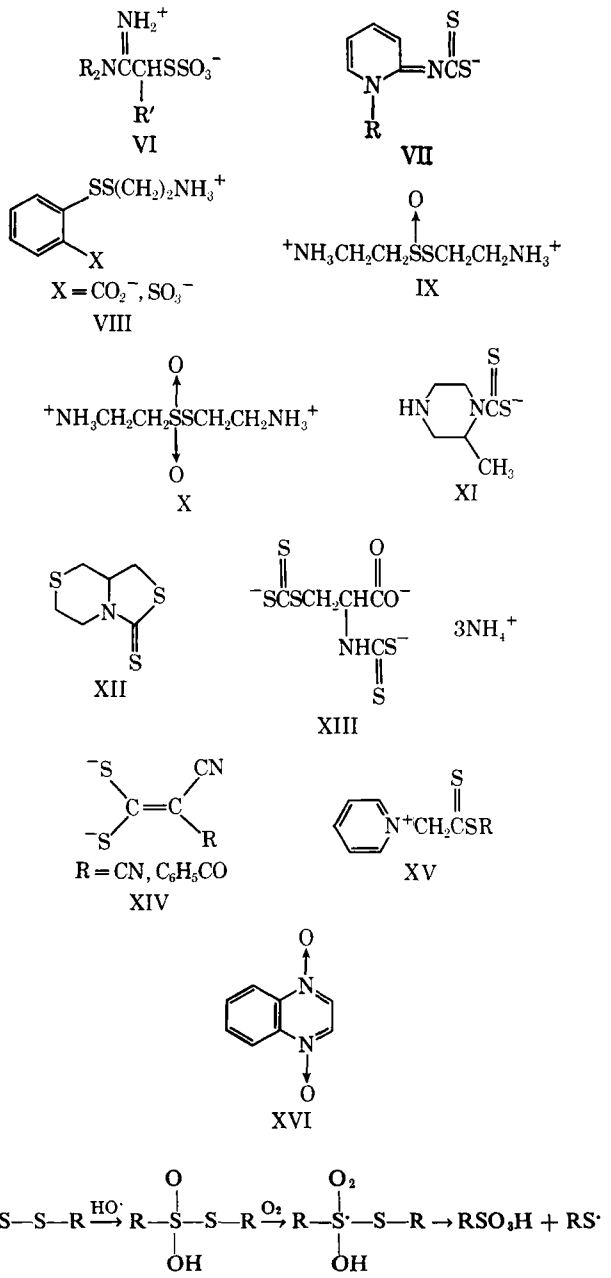
sulfate has sensitized mice with Coker sarcoma 180 (285). The methods used for increasing radiosensitivity of tumors, both chemical and physical, have been reviewed (286).

MECHANISMS OF PROTECTIVE ACTION

The manner in which mammalian cells are protected from the damaging effects of ionizing radiation is not known in complete detail, although evidence is accumulating for several postulated pathways of radioprotection. Protection by means of radical trapping or antioxidant action, which can be demonstrated for simpler systems, such as polymers, may be operative in animal or plant cells as well. It is also probable that other mechanisms are important in protection of cells, and that more than one mode of protection may be possible for a given type of agent. A number of the pharmacologic and physiologic agents described are believed to protect by anoxia; the evidence for this has been discussed (18).

Inhibition of Free Radical Processes—Most of the mechanisms of radioprotection proposed may be grouped under three headings: (*a*) inactivation of free radicals, including peroxides; (*b*) production of cellular hypoxia or anoxia; (*c*) reaction with cellular components. Mechanisms involving free radicals, or "radical scavenging," are based on the assumption that the free radicals resulting from radiolysis of water are the main cause of radiation damage in the cells. Radioprotectors then react with these radicals, of which H·, OH·, and HO_2· are known radiolysis products, and prevent chain reactions from proliferating and ultimately damaging biologically important molecules. This concept received support when a correlation was found between the protective action of about 100 substances in two systems: an aerated aqueous solution of polymethacrylate and the mouse (87). It is probable that radical scavenging is the primary event in the prevention of the polymer from depolymerizing (287), and much evidence favors this mechanism for a number of protective agents in the animal cell, but it is probably not the only event leading to prevention of cellular damage. One argument against this mechanism is that the presence of free radicals in mammalian cells has not yet been demonstrated (18); they have been found in yeast cells, however. In the latter system, sulfhydryl protectors decreased the total number of radicals, but did not appear to protect the cells from the radicals arising from radiolysis of water (288).

Evidence in favor of the activity of some protective agents as inhibitors of free radical processes has been recently reviewed (289). Chemical evidence that MEA acts as a free radical acceptor, as well as oxygen scavenger, has been found in the inhibition of hydroxylation of tyrosine (290) and from X-irradiation of aqueous solutions of cystamine (291) (Scheme II). In preventing oxidation of methyl oleate, MEA reduced the peroxide level of the system, but was not believed to react with other radicals (292). In protection of bacterial cells by MEA, reduction of biological radicals was correlated with increased bacterial survival (293); *S*-type radicals, however, were not found. In this case, MEA was



Scheme II—Radical accepting and oxygen scavenging by cystamine [Jayson et al. (291)].

protective both in the presence and absence of oxygen; others believe that in presence of oxygen, MEA forms a sulfoxy radical which does not react with radicals (294). Protection of trypsin with peptides was attributed to scavenging of radicals produced by radiolysis of water (295, 296). Reaction rates with free radicals formed on protein and peptide molecules have been measured for a number of radiation protectors; the fastest rates were observed for diethyldithiocarbamate, MEA, and cysteine (297) (Table II). Probit analysis also indicated MEA to be a radical scavenger (298). Cysteine and glutathione were found to accept electrons from irradiated proteins, whereas cystine and some nonsulfur compounds did not (299).

A number of antioxidant phenols, pyridines, and gallic acid esters are believed to be effective by virtue

Table II—Reaction Rates of Radioprotective Substances with Serum Albumin- and Glycyltryptophan-Free Radicals[a]

Radioprotective Substance	Reaction Rate, Serum Albumin	l./mole sec. Glycyl-tryptophan
2-Mercaptoethylamine	4.6	10.6
Thiourea	2.9	4.4
Cysteine	2.6	10.4
2-Aminoethylisothiuronium HBr	1.7	3.3
3-Aminopropylisothiuronium HBr	1.6	1.8
Glutathione (reduced)	1.3	3.5
Propyl gallate	1.2	0.4
Diethyldithiocarbamate	3.4×10^3	10^3

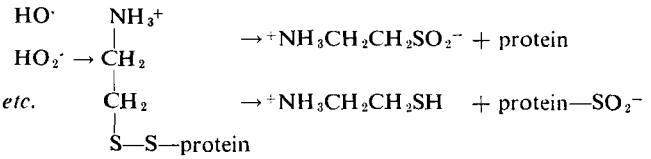
[a] Sapezhinskii and Dontsova (297).

of their antioxidant action. A direct relation between radical inhibitory action and radiation protection has been observed (300). One antioxidant, 3,5-di-*t*-butyl-4-hydroxytoluene protected mice when administered after irradiation (301).

Production of Anoxia or Hypoxia—Protection by producing a state of cellular anoxia or hypoxia is based on the phenomenon of the oxygen effect, the increase by two- to threefold of the damaging effects of radiation due to the presence of oxygen. A number of radioprotective drugs possess the physiological function of producing anoxia or severe hypoxia in various tissues. Those drugs that most likely involve this mechanism include the catecholamines, histamine, choline esters, PAPP, morphine, ethyl alcohol, and nitrite. Other effects may also contribute to their protection; in the case of serotonin, other effects appear to be of equal importance. Although the powerful protection afforded by this compound is not completely explained, a correlation between vasoconstrictive effects and radioprotection was found for a series of indole amines (302).

Radioprotective doses of cysteine, MEA, and AET in mice, however, decreased O_2 consumption in proportion to their protective efficiencies (303). Although the sulfhydryl compounds are capable of consuming oxygen, no apparent hypoxia exists during the period they are protective (304). Postirradiation exposure of rats to respiratory inhibitors reduced mortality and prevented loss of nuclear structure from thymocytes (305). In regard to the effect of regenerating tissues on oxygen tension, they apparently produce large amounts of catalase, which can inactivate $OH^\cdot$ and $HO_2^\cdot$ radicals as well as remove peroxide (306). In this connection, the increase in fibrinolytic and catheptic action of tissues caused by radiation can be decreased by proteolytic enzyme inhibitors (307). Use of iniprol and E-aminocaproic acid decreased lethality of irradiated rats and normalized tissue fibrinolytic activity as well.

Mixed Disulfide Hypothesis—Radioprotection by interaction with cellular components has been postulated for thiol groups of proteins, metal ions, enzymes, and DNA. The "mixed disulfide" hypothesis of Eldjarn and Pihl (308) proposed that radioprotective thiols form mixed disulfides with thiol groups of proteins, and the resulting disulfide could offer at least partial protection to the protein from either free radicals or direct radiation energy (Scheme III). A number of arguments with this hypothesis have arisen; many



Scheme III—Protection by mixed disulfide formation [Eldjarn and Pihl (308)].

thiols do not protect, and almost all of them form mixed disulfides (309); and many proteins are not damaged seriously by a dose of radiation lethal to mammals (310). However, enzymes localized in the cytoplasm, mitochondria, and lysosomes are released into the plasma by the presence of MEA (311), which possibly involves mixed disulfide formation.

Release of Cellular Thiols—Cellular interactions by some radioprotectors also lead to a large increase in endogenous thiol groups. This increase has been reported for aminothiols, cystamine, serotonin, and hypoxia-causing compounds, as well as for the anoxic state (312). This increase in cellular thiol content is 30–40-fold greater than the thiol supplied by the protective agent, in the case of the aminothiols. It has also been observed with diethyldithiocarbamate, but not with its disulfide, disulfiram, which is not radioprotective (313). These observations support the postulation of Bacq that flooding of mammalian cells with a thiol or disulfide causes liberation of thiol-containing substances, such as enzymes and glutathione (314). Mixed disulfide formation may precede this release, radiation protection then resulting from repair by proton transfer from thiols to radicals, particularly in regard to carbohydrate utilization (315). Normal cellular thiol-disulfide equilibria may then be slowly reestablished. An alternative function for the glutathione released is the elimination of H_2O_2 *via* the glutathione peroxidase pathway (316).

Protection of Enzymes—Protection of enzymes by radiation protectors has been reported in numerous instances. The idea of radiation protection by preserving from radiation damage catalase and other enzymes that can remove peroxides and other harmful radiolysis products has been advanced (317). It is believed, at least for some of these enzyme protections, *e.g.*, in the case of catalase (318) and lactic dehydrogenase (319), that the protective agent is complexing the metal constituent of the enzyme and protecting it from radiation-induced oxidation or reduction. It should be noted, however, that radiation doses lethal to mammals are not damaging to some enzymes, and in some cases are actually enzyme-stimulating (320). Catalase is apparently affected by 500 r (X-rays) and is protected in mice by glycine (321). The aminothiols are active inhibitors of catalase (322), and a correlation has been found between extent of radioprotection in mice by thiols and degree of inhibition of catalase (323). The reactivity of catalase toward hydroxy radicals and the hydrated electron has also been studied (324).

Numerous other enzymes have been protected from radiation damage both in the animal and in the isolated

state; the subject is now too extensive to be reviewed here. Several that may play an active role in radiation protection or recovery may be mentioned, however. Pyrophosphatase and ATPase were protected by glycine (325), peroxidase was fourfold more resistant to X-irradiation as a complex with H_2O_2 (326), antioxidants protected enzyme activity in solutions of transforming DNA (327), and DNase was protected by MEA and AET (328). AET had both a protective effect on RNA polymerase activity in regenerating rat liver and a delaying effect on its neosynthesis (329).

The effect of X-rays on the stromal enzymes ATPase, diphosphoglycerate phosphatase, aldolase, nucleoside phosphorylase, and acid phosphatase could be partly duplicated with reducing agents, including MEA, that suggesting radiation damage may be due to reduction of -S-S- bridges (330). However, yeast enolase (void of SH or -S-S- groups), rabbit muscle enolase (containing SH groups), and lactic dehydrogenase (containing SH groups at the active site) were all protected by cysteine and MEG (331). In this case, radiation damage, and protection, did not appear to be a function of SH groups. Protection of enolase and lactic dehydrogenase by enolase substrate, D-glyceric acid 2-phosphate, and by cytidine-2′3′-cyclic phosphate, substrate of ribonuclease, was believed to be due to radical scavenging rather than enzyme binding (332).

Role of Metal Ions—The role of metal ions in radiation damage and protection is not clear, but a number of observations have shown metal ions to be involved in these processes. Several correlations between metal-binding ability and radiation protection have been found, most importantly for the aminothiols (333) and some common metal-binding agents (334) with copper ion. It is also known that irradiation induces metal-ion release in cells, which causes structural changes in nucleic acids and influences enzyme systems (335). Radiation death of *L. delbrueckii*, which was found to be due to the H_2O_2 formed on irradiation, was prevented by addition of catalase. Death was also prevented by EDTA, indicating that the H_2O_2 oxidation, leading to radiation damage, is catalyzed by metal ions (336).

Radiation-protective properties of heavy metal ions are also known; ferrous and ferric ions protect plants (337) as well as trypsin (338). A number of metal ions (ferrous, ferric, cobaltous, mercurous, and cupric) lowered radical concentrations of trypsin and reduced cysteine sulfur radicals (339). All of these ions, except mercurous, protected trypsin. Cupric ions have a protective effect for ribonuclease (340), but are sensitizing for α-amylase and catalase (341). Manganous and ferric ions also sensitized catalase (341). It is also revealing that radiation-induced oxidation of cytosine and uracil produced radicals, but in the presence of cupric or ferric ions, the organic radicals did not result (342*a*). MEA gives similar protection to the pyrimidine bases (342*b*).

Mechanisms of radiation protection which involve the binding of metal ions have been proposed: these include the scavenging of ions of copper or iron to interrupt cellular oxidations initiated by radiation (343), the stabilization of the valence state of copper in copper-containing enzymes (344), and protection of metals bound to enzymes from radical attack by transient complexation by the protector (115, 345). A correlation appears to exist between the copper contents of different mammalian species and their radiosensitivity (346); and cellular copper-containing molecules undergo radiolytic damage preferentially to other molecules (347).

Another effect of metal ions which may be radioprotective is stimulation of mitosis by calcium and magnesium ions (348). Raising calcium levels in rats, either by injection of salts or by parathyroid hormone, increased survival (349).

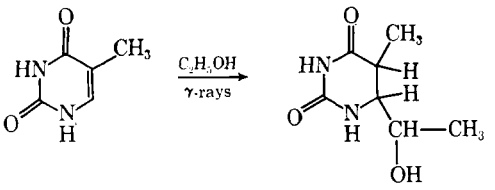
Uncoupling of Oxidative Phosphorylation—The aminothiols can apparently suppress or uncouple oxidative phosphorylation in mitochondria, and this effect as a possible radioprotective mechanism has been reviewed (350). On the other hand, radiation death of cells has been attributed to uncoupling of phosphorylation, leading to accumulation of phosphate in histones with resulting loss of nuclear structure and inhibition of enzymes (351).

Repair by Proton Donation—Repair of damaged molecules by donation of protons to radical sites of biological molecules has also been postulated as a protective mechanism for the aminothiols (352) (Scheme IV). Radical formation of a macromolecule, such as trypsin, can lead to cross-linking, in absence of O_2, or to peroxy-radical formation in presence of O_2. Thiols can compete with O_2 for reaction with free radicals and restore the macromolecules to their normal state. The interference of O_2 with the radioprotective effect of thiols becomes apparent with this explanation. Evidence for it has been provided by irradiation of viruses which contain no SH groups and show no interference of repair by O_2 (353). Also, the appearance of RS· radicals was seen (by ESR) only in absence of O_2. And in experiments with bacteria, O_2 converted MEA to the sulfoxy radical and prevented its protective effect (294).

Binding to Nucleic acids—Another mechanism of radio protection postulated for the aminothiols, for which good evidence exists, involves the ability of their disulfides to bind reversibly to DNA, RNA, and other nucleoproteins (354). This leads to two effects: first, the loose ends of the helix resulting from single-strand rupture are held in place so that shortening or alteration of the chain is prevented; and second, DNA replication rate is decreased so that a repair process can occur before alterations are replicated (355). This, together with the repair mechanism stated above, accounts quite well for the protection by the aminothiols of the nucleic acids, regarded by some as the site of primary radiation damage. It also requires that the disulfide is the active form of the thiol-protective agent, and explains why more than a three-carbon chain leads to inactive aminothiols [*e.g.*, $NH_2(CH_2)_4SS(CH_2)_4NH_2$

$RH \rightarrow R\cdot + H\cdot$	(irradiation)
$R\cdot + R\cdot \rightarrow R - R$	(crosslinking)
$R\cdot + O_2 \rightarrow RO_2\cdot$	(peroxidation)
$R\cdot + R'SH \rightarrow RH + R'S\cdot$	(protection)
$R'SH + O_2 \rightarrow R'SO_2H$, *etc.*	(competition)

Scheme IV—Radical repair by thiols [Bacq and Alexander (352)].



Scheme V—Radiation-induced addition of ethanol to thymine [Brown et al. *(358)].*

has just the length where binding to DNA falls off]. Other structural requirements of the aminothiols may also be explained by DNA binding, *e.g.*, the ability of acylthioesters to undergo disulfide formation, as well as the phenomenon of radiosensitization by closely related thiols which may bind in a less reversible fashion.

DNA has also been protected by thiourea and propyl gallate, as well as by cysteine and cystamine, apparently by antioxidant effects (356). Protection of DNA from radicals produced by H_2O_2 and ferrous ion was also provided. Others believe that the protection of DNA by bound GED is due to localized radical scavenging (357).

An explanation of the protective effect of ethanol, and other hydroxy compounds, arose from the observation that ethanol adds to thymine under γ-irradiation (358) (Scheme V). This prevents formation of thymine dimers, deleterious to DNA. It also explains the radiation resistance of bacterial spores, and protection of bacteria in glucose medium, where hydroxy compounds are in adequate supply to undergo addition to thymine.

An observation relating O_2 toxicity, ionizing radiation, and aging has been made (359). Both O_2 and ionizing radiation produce free radicals leading to lipoperoxides, which also take part in the aging process. Antioxidants, compounds which provide labile H, including radiation-protective agents, and the hexose monophosphate shunt, all serve to counteract this process. Those who have helped develop or explain radioprotective agents may thus be contributing to unexpected fields of investigation. It has been suggested that prophylactic doses of antiradiation agents may prevent aging in cells (360).

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