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(12)

RADIOPROTECTIVE AGENTS

The discovery of x rays by Roentgen in 1895 and the isolation of the highly radioactive element radium by the Curies in 1896 were the two events that marked the beginning of the nuclear era. The ability of x rays to penetrate human tissue was appreciated immediately as a potential medical asset, and they were put to use enthusiastically. Early workers did notice an erythematous reaction when skin was exposed to the rays for lengthy periods of time. Later, lesions of the skin and cancer of the bone, primarily in the extremities, developed in some scientists, physicians, and patients receiving high doses of x rays. For centuries prior to this period, workers in the mines from which the Curies had obtained pitchblende ore for their radium isolation experienced a high incidence of lung cancer. Uranium miners in the Colorado Plateau were similarly afflicted.

The death, suffering, and permanent damage inflicted on many people by high levels of radiation incurred by the dropping of atomic bombs on Hiroshima and Nagasaki in 1945 stimulated research in several countries, notably the United States, the USSR, France, the United Kingdom, Canada, the Federal Republic of Germany, and Japan, to find the chemical agents that would minimize the effects of radiation.

In an early experiment performed under the Manhattan Project, it was discovered that an irradiated sulfur-containing enzyme could be reactivated by the addition of cysteine; this suggested that radioprotection of biological systems was possible. Several thousand compounds, mainly sulfur containing, have since been designed, synthesized, and tested in animals, mostly rodents. When administered in advance of irradiation, many of them show excellent ability to prolong the life of animals subjected to lethal radiation. In humans, some of the more promising radioprotective agents are being considered as adjuncts in cancer radiotherapy and chemotherapy.

A discussion of the biological effects of ionizing radiation is given in refs. 1–10. Reviews and compendia relating to chemical radiation protection also are available (11–22). The application of radioprotective agents to the treatment of cancer is described in ref. 23.

Biological Aspects of Radiation Damage

The Nature of Radiobiological Injury. The sequence of events leading from the initial absorption of radiation energy to the ultimate death of the organism is complex and incompletely understood. It is convenient to divide the process of radiation injury into events occurring at the molecular level, at the cellular level, and at the level of the organism. The following discussion is limited to the biological effects of high energy photon sources, ie, x and γ radiation of >200 kV_p (kilovolts peak). When high energy photons interact with molecules in biological systems, the initial relevant event is the production of Compton electrons, which interact with adjacent molecules to produce secondary electrons. It is these electrons that are primarily responsible for the initiation of radiation damage.

Molecular Level. The interaction of radiation with molecules in biological systems can be divided into direct action and indirect action. Direct action results when radiation energy is deposited in a target molecule and causes damage without the participation of mediators. In indirect action, radiation energy is deposited in the vicinity of a target molecule, and damage is transferred to the target by free radicals. Absorption of radiation by biological solvent molecules, followed by reaction of the radiolysis products of water with solute molecules, is the usual example of indirect action in biological systems. However, even in nonaqueous regions of such systems, there are few cases where secondary transfer of radiation energy, ie, indirect action, is not involved.

When a molecule in a biological system undergoes initial interaction with secondary electrons, it is either excited or ionized. When an electron is ejected from the molecule, a radical cation forms. Conversely, when such an electron is trapped, a radical anion forms (24). These primary ion-radical species then undergo transformations, eg, decarboxylation, deamination, and disulfide bond rupture, whereby deposited energy is transferred *inter-* or *intra*molecularly with the formation of semistable neutral bioradicals. The resulting molecular alterations may lead to the loss of the target molecule's ability to perform its particular biological role. These steps can be summarized:

$$RH \rightsquigarrow RH^{\cdot +} + e \quad (1)$$

$$RH + e \rightarrow RH^{\cdot -} \quad (2)$$

$$RH^{\cdot +} \rightarrow R^{\cdot} + H^{+} \quad (3)$$

In oxygenated systems

$$R^{\cdot} + O_2 \rightarrow RO_2^{\cdot} \quad (4)$$

In the presence of an endogenous or exogenous sulfhydryl

$$R^{\cdot} + RSH \rightarrow RH + RS^{\cdot} \quad (5)$$

Such symbolic reactions suggest one way in which molecular oxygen can act as a radiosensitizer by preventing the reversal of the first reaction (see eq. 1), ie, fixing radiation damage by peroxy-radical formation (see eq. 4). Donation of a hydrogen atom (see eq. 5) by a thiol could result in instantaneous repair of the radical lesion formed in equations 1 and 3.

When a biological target molecule is considered in its *in vivo* environment, numerous factors may influence the mechanism of its damage by ionizing radiation. It

may be located in a principally aqueous phase of a cell where its inactivation would be mediated by the processes of indirect action, in which the primary radiolysis products of water, ie, $H^{\cdot}$, $OH^{\cdot}$, and e_{aq}, are the damaging species. At the other extreme, it might be in a cellular region where other molecules like itself surround it, ie, in a nonaqueous environment approaching a solid-state system. Here, the processes of classical direct action and solid-state energy transfer could lead to its inactivation. These potential environmental extremes in the living cell encompass numerous variations which must be considered, especially when simplistic models are used to relate *in vitro* findings in well-defined model systems to findings in cell culture or *in vivo*.

With cautious interpretation, model systems for the study of molecular-level mechanisms of radiation damage can be extremely valuable. Reactions of water radicals with biomolecules are most frequency studied by pulse-radiolysis techniques (25–26), by spin trapping (27), or in esr studies in which frozen matrices are used to slow the interaction processes (28). One can determine which of the water radicals is most damaging to a particular macromolecule in dilute aqueous solution. Molecular-level investigations of single crystals or powders can lead to an understanding of the mediators of energy transfer in the solid state.

Cellular Level. Within the living cell, the dynamics of cell biochemistry and metabolism are superimposed on molecular-level interactions. Radiation inactivation of a single molecule can be transferred to other types of molecules through coupled reactions (29). If a number of molecules altered by radiation-induced rearrangements were involved in a common coupled reaction, there could result a marked enhancement of radiation damage suffered by dependent reactions. Radiation damage to DNA or RNA can result in the synthesis of inactive biological macromolecules, thereby, markedly amplifying the initial radiation damage. Disruption of subcellular organelles, such as chromosomes, microsomes, or mitochondria, can result in malfunction. Experimental evidence indicates that although both direct and indirect effects can contribute to the injury of mammalian cells, it is probably indirect action mediated by the hydroxyl radical that is most damaging to critical macromolecules of cells (30–31).

Identification of the critical site or macromolecular target whose damage is primarily responsible for cell injury has been the goal of extensive investigations. It is generally agreed that this target is in the cell nucleus (32) and that a principal target molecule in mammalian cells is DNA (33–34). Biological effects other than cell death, such as gene malfunction and chromosome aberration, are also related to DNA damage (35). Other important candidates for the cellular target include membranes of the cell, the nucleus, and the other cellular organelles (36–37) and sulfhydryl- and disulfide-containing biological molecules (38).

Radiation-induced cell death may be broadly separated into two classes: reproductive death, ie, where cell division is involved, and interphase death, ie, where cell death does not involve mitosis. Interphase death usually follows very high radiation doses [>200 Gy (>20 krad)] and may be related to impairment of membrane permeability, reduced ATP (adenosine triphosphate) synthesis, and nuclear disorganization, but the precise mechanism of cell death is unknown. Reproductive death of cells has been defined as the loss of reproductive integrity with subsequent loss of metabolic activity and cellular functions and may result from low radiation doses [<10 Gy (<1 krad)] (39). Death of the cell may take place on the first or second attempt at division and appears to be primarily the result of chromosome aberration (40).

Mammalian-cell radiosensitivity is not constant during the various stages of the cell cycle, but is generally greatest immediately before, during, and immediately after mitosis (40–41). When the radiation dose rate is lowered sufficiently, many of its damaging effects are considerably diminished, even though the same total radiation dose is given. Similar effects are observed in fractionated irradiation, in which the interval between irradiations is increased. Repair or recovery mechanisms have been proposed to explain such phenomena, and they generally consider repair of sublethal damage and circumvention of additive effects (42–45). Repair of sublethal damage to mammalian-cell DNA includes such processes as excision repair and postreplication repair (46). The nucleases involved in such repair processes must be considered as important radiation target molecules that have a significant role in modification of reproductive death. At low dose rates and when there is sufficient time between divided radiation doses, they may mediate recovery from sublethal or even lethal doses.

Organism Level. It is useful to categorize tissues in three classes, according to their rate of cell division (in order of increasing radiation sensitivity): steady-state populations, eg, adult nerve and muscle; expanding populations, eg, liver and kidney; and renewing populations, eg, bone marrow, thymus, spleen, and intestinal-crypt cells. Low doses of whole-body irradiation [<10 Gy (<1 krad)] damage stem cells of bone marrow and lymphoid tissue. Death from such radiation dose levels usually results from hemorrhaging, infection, or anemia; it follows 7–30 days after exposure and is termed hematopoietic death. At doses of 10–100 Gy (1–10 krad), intestinal-crypt cell renewal is inhibited; thus, before the elements of hematopoietic death are manifested, gastrointestinal death occurs 3–6 d after exposure. At that time, intestinal-crypt cells have been depleted with a fatal loss of electrolytes and water. If extremely high radiation doses are administered, ie, >200 Gy (>20 krads), function of the steady-state cells of the central nervous system is sufficiently altered, and CNS death follows within 24 h or even during irradiation, depending on the magnitude of the administered dose.

Evaluation of Potential Radioprotective Agents. Numerous preliminary questions must be answered before a potential antiradiation agent can be tested for efficacy. These include selection of the appropriate radiation type and dose level, the test organism, the meaningful end-point parameter, the drug dose and route of administration, the time separation of drug administration and irradiation, and the statistical method by which data are analyzed. Organism death is usually selected as the end point to judge antiradiation effectiveness, although numerous other radiobiological lesions have been used (47–51). Data derived from end points other than organism death are usually correlated with mammalian death. Because of the large number of animals required for the statistical analyses of screening results, the mouse is the most commonly used animal model.

The optimum dose of the potential radioprotective drug must be derived from toxicity studies with the same type of test animals. The drug dose that is lethal to half of a group of animals in 14 d ($LD_{50/14}$) is determined, and from this a maximum tolerated dose (MTD) is selected, usually as ½–⅔ the $LD_{50/14}$. A radiation dose is selected that is just sufficient to kill all control animals in 30 d ($LD_{100/30}$). This dose is ca 5–10 Gy (500–1000 rads) for most mammals. Control animals receive equivalent volumes of the carrier or solvent and are exposed to irradiation simultaneously with the treated animals.

The optimal time between drug administration and irradiation must be deter-

mined empirically but is based on the suspected mechanism of protection involved and on the probable absorption time by the route of administration. In mice, this time is 15–30 min after ip (intraperitoneal) injection and 30–60 min after oral intubation. Each radioprotector has a characteristic time-interval optimum. For example, whereas 2-mercaptoethylamine [*60-23-1*] (MEA) protects irradiated human cells in culture maximally ten min after administration, the sulfhydryl form of the phosphorothioate WR 2721 [*20537-88-6*] protects optimally at ca 100 min; WR 2721 shows maximal protection after still longer times (52). Numerous additional factors affect the protective interval *in vivo* (53–54).

Although numerous indexes have been employed to describe the magnitude of chemical protection against radiation damage, the two most commonly reported are modifications of the percent survival and the dose-reduction factor (DRF) or dose-modification factor (DMF). The first is the percentage of irradiated animals that survive a particular dose of radiation for a certain time, usually 30 d, and is most useful in preliminary screening. For critical comparison studies, the DRF or DMF is employed. The dose-reduction or modification factor is the ratio of radiation doses administered to protected and control animals that produces the same biological effect in both animal groups. Again, the usual practice is to use organism death as the end point, but other parameters, including endogenous spleen-colony counts, have been employed (51). Thus,

$$\text{DRF} = \frac{\text{LD}_{50}\ \text{protected}}{\text{LD}_{50}\ \text{unprotected}}$$

where the LD_{50} may be determined at any selected time interval. When another end point of biological effect is selected, it is essential that an identical biological effect common to experimental and control animals can be identified.

Theories of Protection. ***Molecular Level.*** *Radical Scavenging.* To the extent that the radiolysis products of water play a role in the cause of cell injury in mammalian systems, the ability of radioprotective compounds to scavenge these mediators of the indirect effect must be considered a relevant mechanism in radioprotection. Moreover, since there are few examples in biological systems where radiation damage is mediated solely by the direct effect, it is axiomatic that scavenging of free radicals should at the very least be a contributing mechanism of radiation protection. However, even excellent $OH^{\cdot}$ scavengers, eg, MEA or ethanol, which react with the hydroxyl radical at essentially diffusion-controlled rates, must be present *in vitro* at 10 m*M* and 1 *M* to assure minimal and good protection, respectively, of macromolecular function (30–31). On the other hand, if MEA is assumed to be distributed uniformly in the aqueous phase of the cell at a concentration of 3 m*M*, it gives excellent protection against radiation-induced cell death (30). This indicates that some phenomenon must be responsible for concentrating the protector at the site of critical target macromolecules by approximately a factor of 100 above that predicted from a uniform distribution of protector in cell water. Although this requirement is frequently overlooked, it has been the goal of hypotheses of radioprotection to develop mechanisms where this requirement is met so that radical scavenging and hydrogen-atom donation (see below) can be meaningful in the cellular milieu (55).

Model studies involving DNA as the target molecule indicate that the most effective radical-scavenging radioprotectors form some type of complex with DNA and are then able to scavenge radicals at this presumably critical site. For

example, both cadaverine [*462-94-2*] $H_2N(CH_2)_5NH_2$, and WR 2721, $H_2NCH_2CH_2CH_2NHCH_2CH_2SPO_3H_2$ (or its *in vivo* sulfhydryl form) bind to DNA. However, presumably because WR 2721 can also scavenge $OH^{\cdot}$ at a diffusion-controlled rate, it protects DNA from radiation damage, whereas cadaverine does not (56). DNA binding is not a universal requirement for radioprotection and does not correlate with radioprotective efficacy in the *N*-heterocyclic aminoethyl disulfides (57). Sulfur-containing radioprotective compounds are also excellent scavengers of hydrogen atoms and hydrated electrons, which are two other significant water radicals.

Hydrogen Transfer. A second fundamental phenomenon, which may account for reduction of radiation damage in biological systems, is indicated by equation 5. If the initial damage to the target consists effectively of loss of a hydrogen atom, then its restoration constitutes instantaneous repair and, thus, protection. Although H-atom transfer has only been observed in model systems (58–60), studies of mammalian cells in tissue culture have, by analysis of the shape of survival curves, resulted in the identification of two types of protection: competitive and restitutive (61). Existence of shoulders in such curves probably indicates protection involving competition for radiation products, ie, scavenging, whereas displacement of linear survival curves, which are observed after irradiation with high LET (linear energy transfer) particles, is thought to indicate repair of radiation lesions, perhaps by H-atom transfer. As in the case of radical scavenging, some mechanism must be invoked to account for localization of H-atom donors at critical sites.

The Mixed Disulfide Hypothesis. In one explanation of radioprotectant localization, it is proposed that the aminothiol protectors form temporary mixed disulfides with —SH and —SS— groups within cells (62–64). If the mixed disulfides were attacked by either direct- or indirect-radiation action, in at least half of such encounters radiolytic scission of the disulfide bond would restore the originally covered sulfhydryl moiety or allow restoration of a disulfide bond. Times for formation of mixed disulfides *in vivo* correspond well with times of observed optimal radiation protection, and good protectors exhibit the better propensities for mixed disulfide formation. The most protective sulfur compounds are probably able to induce polarization of the temporary mixed disulfide bond and, thereby, increase the probability that the S atom receiving the radiation insult would be that contributed by the protector to the mixed disulfide bond, which accounts for greater than 50% protection.

This hypothesis provides what is perhaps the most attractive postulate to account for localization of protectors at specific sites. However, since DNA has no —SH and —SS— moieties, it would seem that the mixed-disulfide hypothesis does not apply to protection of what has been considered the most important target macromolecule. Subsequent studies indicate that mixed-disulfide formation with nuclear proteins could, in part, account for the required enhanced concentration of potential radical scavengers and H-atom donors in the vicinity of DNA (65). Also, to the extent that cellular membranes constitute the target of ionizing radiation, the mixed-disulfide hypothesis becomes increasingly relevant (66).

Endogenous Nonprotein Sulfhydryl Compounds. A second hypothetical mechanism for localization of sulfur-containing radioprotective compounds at critical sites has been proposed (67–68). This hypothesis, like the former, involves the formation of temporary mixed disulfides between exogenous sulfhydryl radioprotective compounds and cellular disulfides; however, the subsequent focus of this concept is on the glutathione [*70-18-8*] or other nonprotein sulfhydryl (NPSH) species released

when the temporary disulfide forms. The hypothesis suggests that it is the released endogenous sulfhydryl that scavenges water radicals. Thus, the NPSH hypothesis could account for protection of any cellular macromolecule, eg, protein, membrane constituent, or nucleic acid, exposed to increased concentration of released endogenous sulfhydryl. The fundamental observation on which the hypothesis is based is the correlation of increase in cellular sulfhydryl concentration induced by radioprotectors with their radioprotective efficacy. Compounds such as *N*-(2-mercaptopropionyl)-glycine [*1953-02-2*], with little ability to bind to DNA, protect DNA against single-strand breaks as effectively as MEA (69), which suggests that the shared ability to displace GSH (reduced glutathione) could be responsible. Enhanced protection by a combination of sulfur and nonsulfur protectants indicates cooperative effects in nonprotein thiol release (70). However, the postulated released endogenous scavenger, glutathione, is not a particularly effective radical scavenger (25–26). Moreover, selective oxidation of NPSH prior to irradiation does not enhance cell radiosensitivity (71). What differentiates the two mechanisms is the question of whether critical reactions of radiation damage occur primarily within the sphere of influence of the temporary mixed disulfide or in regions where only scavengers released from this zone are effective. It is probable that both hypotheses have relevance in chemical radioprotection.

Physiological-Biochemical Level. It is important that a mechanism of radioprotection not be sought at the molecular level when a far more critical mechanism of protection operates at a higher level. A reduction in body temperature is often associated with administration of various radioprotectants (72). A suggested mechanism for protection by hypothermia is that, during the period of lowered temperature, a reduced metabolic rate permits repair of crucial radiation damage before the demand of normal metabolism returns. Whereas such phenomena may be involved in protection by phenothiazines (73), hypothermia is usually considered only a side effect for the sulfur-containing radioprotectants.

Prevention of reactions involved in the oxygen effect (see eq. 4) is the apparent mechanism by which a number of compounds, particularly those related to histamine, are thought to be capable of protection. Drugs can induce hypoxia by either blocking hemoglobin function, increasing tissue oxygen utilization, or reducing local blood flow. Involvement of hypoxia in the mechanism of a compound's protection can be tested by irradiation under high oxygen pressure where the compound's hypoxic effects would be overwhelmed. Sulfhydryl radioprotective compounds maintain their efficacy under such conditions.

Administration of compounds that result in the release of interferon [*9008-11-1*] endogenously or of interferon itself has been reported to increase radioresistance of animals, if the effects of interferon were maximal at the time of irradiation (74–76). Although the mechanism of interferon protection is uncertain, it may involve an interruption of progression through the cell cycle at the most radioresistant stages. It may also induce the release of endogenous thiols (75).

Chemical Radioprotective Agents

Thiols. Cysteine. The vast majority of antiradiation agents are aminoalkyl thiols or derivatives thereof, the prototype of which is the sulfur-containing amino acid cysteine [*4371-52-2*] (1).

(1)

This compound protects 75–89% of rats subjected to 8 Gy (800 rad) if it is administered 5 min prior to x irradiation at 175–575 mg/kg (77). In this study, 19% of the irradiated control rats survived. Cysteine is equally effective if given up to one hour before irradiation. Mice given 1000 mg/kg of cysteine iv (intravenously) are protected to the extent of 50% from the effects of lethal radiation (78–79). Chromosome damage in irradiated human bone-marrow cells has been reduced 58% by cysteine (80).

A number of carboxylic esters of cysteine have been reported to give good protection, in terms of percent survival, to rats (81): cysteine methyl ester hydrochloride [*2485-62-3*], 70%; cysteine ethyl ester hydrochloride [*3411-58-3*], 55%; cysteine propyl ester hydrochloride [*60654-26-4*], 100%; cysteine isopropyl ester hydrochloride [*73255-49-9*], 40%; cysteine butyl ester hydrochloride [*60654-27-5*], 60%; cysteine isobutyl ester hydrochloride [*81643-70-1*], 100%; and cysteine isoamyl ester hydrochloride [*81643-71-2*], 70%. The oxidized form of cysteine, namely, cystine, and its diethyl ester impart no protection (77–78).

A reaction between cysteine and rutoside gives rutosidyl-2′-methylenecysteine, which is claimed to normalize serum-protein fractions in x-irradiated animals (82).

Interchanging the positions of the NH_2— and HS— groups of cysteine gives isocysteine, which has no radioprotective properties (83).

2-Mercaptoethylamine. The decarboxylated form of cysteine, namely 2-mercaptoethylamine (2) (MEA, cysteamine, 2-aminoethanethiol, mercamine, Becaptan) is an even more promising antiradiation agent than cysteine (84).

(2)

2-Mercaptoethylamine, as the free base, is readily air-oxidized to its disulfide and probably exists in the zwitterionic form $H_3N^+CH_2CH_2S^-$ (see Sulfur compounds; Thiols). The latter concept is borne out by the unusual situation wherein the free base of MEA melts at a higher temperature (97–98.5°C) than its hydrochloride salt [*156-67-0*] (70–71°C). The hydrochloride salt of (2) is less susceptible to air-oxidation than the free base and is the form in which it is generally stored and administered.

Because of its structural simplicity, MEA hydrochloride is one of the most studied antiradiation agents. It is the compound that not only serves as a model for the design of other agents, but generally is also the standard by which the activity of other agents is judged. The compound confers greater protection to mice irradiated with a single 8-Gy (800-rad) dose than to the mice given four 2-Gy (200-rad) doses at intervals of 7 d (85). It offers protection against at least 3 repeated lethal exposures, provided they are at 30-day intervals (86). When administered in the drinking water of mice, MEA did not protect against chronic radiation (87). The compound protects the gastrointestinal tract and bone marrow of mice (88).

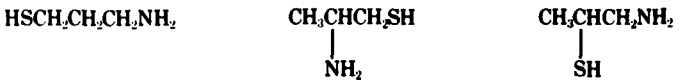
The antiradiation properties of MEA are optimized in mice if it is given 10 min prior to radiation (89), whereas in rats, best results are obtained 45 min before radiation (90). 2-Mercaptoethylamine protects mouse (91–92) and rat (93–94) spermatozoa. In the rat fetus, it prevents foot deformities and gait defects in the progeny if admin-

istered to mothers irradiated on the 14th day of pregnancy (95). Also, it reduces learning deficiency in surviving rats irradiated *in utero* (96).

2-Mercaptoethylamine has been prepared in a variety of salt forms, eg, the hydrobromide [*42954-15-4*], ascorbate [*16031-82-6*], nicotinate [*81643-72-3*], salicylate [*81643-73-4*], (97) and tartrate [*18594-39-3*] (98). The first three are more effective and less toxic than the hydrochloride [*156-67-0*] (99–100). Cytriphos (cysteamine adenosine triphosphate) shows a radioprotective effect in mice after both short-term and prolonged irradiation and is less toxic than MEA.HCl (101–103).

The radiation-prophylactic action of MEA has been ascribed to its ability to scavenge free radicals (30–31), to form mixed disulfides (104), to induce hypoxia (105–107), and to prevent cross-linking (108) and DNA breakdown induced by radiation (109).

Other Mercaptoalkylamines. The relative activities of the next higher homologues of MEA, namely 3-aminopropanethiol [*462-47-5*] (3) (3-mercaptopropylamine, MPA), 2-aminopropanethiol [*10229-29-5*] (4), and 1-amino-2-propanethiol [*598-36-7*] (5), are not particularly clear.



(3) (4) (5)

3-Aminopropanethiol is reported to be superior to MEA on a molar basis (78); however, it is also claimed that the same compound is totally ineffective (79,110). Compound (4) is reported to have about the same toxicity as MEA (111). Other investigations suggest that (4) and (5) have a greater prophylactic range than MEA (112). In general, there seems to be agreement that (5) is superior to its isomer (4). Whereas (4) offers protection to only 20% of irradiated mice at a dose of 175 mg/kg (79), (5) gives 60% protection at 300 mg/kg. In one study, (5) offered good protection (113). In another, 57–80% survival in mice and 65–75% in rats was obtained, depending on the administered dosage, but (5) is inactive when administered orally (114). In another report, (5) is judged to be superior to MEA as an antiradiation agent (115).

The placement of more than three carbon atoms between a thiol or a potential thiol and an amino group completely eliminates mammalian radioprotective properties (78,115–117). Other variations that seriously diminish or destroy activity include the alkyl-branched mercaptoethylamines (6) (118), *sec*-mercaptoalkylamine (7) (119), and 2-mercapto-2-phenethylamine [*934-14-5*] (8) (120).

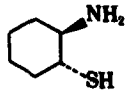
(6) (7)

Penicillamine [*52-67-5*] (9) long thought to be a radiosensitizer (121–122), is protective when administered 1 h before radiation (123).

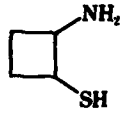
(8)

(9)

The placement of amino and thiol functions at adjacent positions in an alicyclic system, eg, DL-*trans*-2-aminocyclohexanethiol [*20509-06-2*] (10) (124–125) and *cis* and *trans*-cyclobutyl derivatives (11)–(13) (126), yields compounds with considerable antiradiation activity.



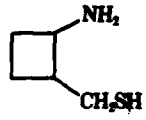
(10)



(11)

cis [*36455-65-9*]

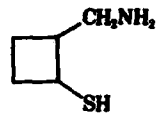
trans [*36455-66-0*]



(12)

cis [*81643-74-5*]

trans [*59276-24-3*]



(13)

cis [*40830-54-4*]

trans [*59273-23-2*]

An extensive series of *N*-alkyl MEAs and 2-hydrazinoethanethiols was synthesized, but none is superior to MEA (127). The *N*-phenethyl- (128) and carboxymethyl- [cysteamine-*N*-acetic acid, (14)] derivatives of MEA have good antiradiation properties.

(14)

cysteamine-*N*-acetic acid

The latter compound and its esters and salts are better tolerated and more effective than MEA (129–131).

N-Acetylation and *N,S*-diacetylation of MEA yields products with only slight activity (132). 2-Carboxyethyl- and 2-carbamidoethyl-*N*-substituted derivatives of MEA have excellent activity if given in high doses (133). 2-Mercaptoacetamidine [*19412-52-3*] (15) and its disulfide [*44957-28-0*], when given *ip* (intraperitoneal) or po (*per os* = oral) to mice prior to exposure to 9 Gy (900 rads) of x rays, increases their survival chances to 50% (134).

(15)

Aminoethyl sulfides (16) that form by *S*-alkylation of MEA tend to have little or no radioprotective activity (36,135–138).

$$H_2NCH_2CH_2SR$$

(16)

However, the increased stability of these derivatives has been reported, and *S*-methyl [*18542-42-2*], *S*-phenyl [*2014-75-7*], *S*-benzimidazoyl [*7673-88-3*], *S*-benzothiazoyl [*60372-30-7*], and *S*-furfuryl [*81643-73-6*] derivatives of MEA have antiradiation activity comparable to MEA (135). A caffeine derivative of MEA is reported to have good activity (99).

S-Acetyl MEA [*6197-31-5*] offers 60% protection to mice when given at 400 mg/kg, but *S*-benzoyl MEA is, for the most part, devoid of activity (139). The trithiocarbonate [*15547-18-9*] (17) protects 75% of irradiated mice at a dose of 350 mg/kg (139–141).

$$H_3\overset{+}{N}CH_2CH_2S\overset{S}{\overset{\|}{C}}S^-$$

(17)

An extensive series of MEA hemimercaptals derived from glycolic acid has been prepared. The most active member is (18) [*32641-24-0*], which protects mice against 8.5 Gy (850 rads) at a dose of one-half its LD_{50} (142).

$$\begin{array}{l} HOCHCOOCH_3 \\ | \\ SCH_2CH_2NH_2\cdot HCl \end{array}$$

(18)

Glutathione [*70-18-8*] (19) is a tripeptide possessing a cysteine moiety and is reported by one group to give moderate radiation protection (143), whereas another group indicates that it is inactive (78).

$$\begin{array}{l} \qquad\qquad\qquad\quad CH_2COOH \\ \qquad\qquad\qquad\quad | \\ \qquad\qquad HSCH_2CHCONH \\ \qquad\qquad\qquad\quad | \\ HOOCCHCH_2CH_2CONH \\ | \\ NH_2 \end{array}$$

(19)

Alkylthiols Lacking an Amino Group. One of the most interesting compounds developed as an antiradiation agent is sodium 2,3-dimercaptopropanesulfonate [*4076-02-2*] (20) (Unithiol), which was first synthesized in the USSR (144).

$$\begin{array}{l} CH_2CHCH_2SO_3Na \\ | \quad | \\ SH\ SH \end{array}$$

(20)

It is more protective and less toxic (LD_{50}, 1400 mg/kg) in mice than MEA (99). It also is protective in rats and dogs. Unithiol is structurally related to the heavy-metal antidote, 2,3-dimercaptopropanol (BAL). In rodents, it is an efficient chelating agent which, when complexed, is eliminated from mammalian systems in water-soluble form. Unithiol has been studied in the treatment of poisoning by mercury (145–146), arsenic (147), antimony (148), gold and cadmium (149), and mixtures of metals, eg, mercury, nickel, copper, and cadmium (150).

Cleland's reagent [*3483-12-3*], which is also a dimercaptan, protects ca 30% of irradiated mice (151–152), whereas its cyclized, ie, disulfide, form [*25902-99-2*] protects 56% of irradiated mice (151–152).

Disulfides and Trisulfides. 2-Mercaptoethylamine can be oxidized to its disulfide, ie, bis(2-aminoethyl) disulfide [*51-85-4*] (cystamine). The free base is a water-soluble liquid; however, it is usually administered as a solution of its crystalline dihydrochloride salt [*56-17-7*] (**21**). The compound has lower acute toxicity, is as about as effective as MEA, and exhibits activity when administered orally to mice, rats, and guinea pigs (153–154).

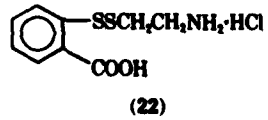
$$(HCl{\cdot}H_2NCH_2CH_2S)_2$$

(21)

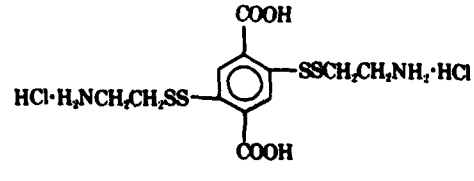
The compound affords 60% survival at a dose of 146 mg/kg to rats subjected to lethal radiation and also protects antibody production in rats (155–156). Cystamine is not effective when incorporated into the diet of mice (157). Cystamine at a dose of 60 mg/kg depresses the clinical signs of radiation sickness in dogs and accelerates their rate of recovery after exposure to 3 Gy (300 rads). The severity of leukopenia is also diminished (158). A clue to its mechanism of action may be in the reduction of cystamine to MEA *in vivo* during irradiation (159). Other beliefs are that cystamine protects DNA by complexing with it, thereby stabilizing the DNA helix (160), and that mobilization of endogenous catecholamines may be involved (161). Recently, a drug called resinamine, ie, cystamine bound to Dowex 50 resin, is claimed to prolong the action of cystamine and to increase its radioprotective effect (162). Cystamine pyrophosphate [*58480-03-8*], when given ip or iv to rats, accumulates in the bone marrow to a greater extent and is more radioprotective than the dihydrochloride salt (163).

None of the *N*-substituted derivatives of cystamine, including a series of *N*-heterocyclic aminoethyl disulfides, exceeds the activity of the parent compound (164). The pharmacology of a few *N,N'*-dialkylated cystamines has been reported (131).

A limited number of aromatic mixed (unsymmetrical) disulfides, eg, *o*-(2-aminoethyldithio)benzoic acid hydrochloride [*1204-52-0*] (**22**), show possible activity (165–167), whereas those obtained from mercaptoterephthalic acid (**23**) fail entirely to protect irradiated animals (168).



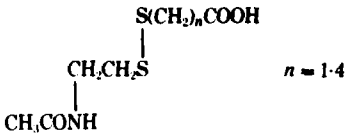
(22)



(23)

Of the totally aliphatic unsymmetrical disulfides of the type exemplified by structures

(24) (169) and (25) (170), the only active compound is (25), where $n = 3$ [*15386-71-7*].



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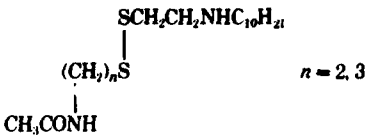
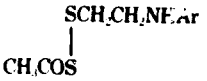


(25)

The mixed disulfides of type (26) give good protection to mice at moderately low doses (171).

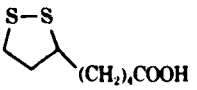


(26)

Since unsymmetrical disulfides tend to disproportionate, especially under alkaline conditions, so as to give a mixture of symmetrical disulfides, it may be that under physiological conditions the combined effects of the symmetrical disulfides are observed.

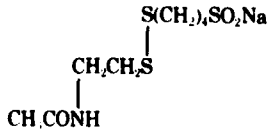
$$2\,RSSR' \rightleftharpoons RSSR + R'SSR'$$

The cyclic disulfide, thioctic acid [*62-46-4*] (27) is reported to be toxic and nonprotective in mice (172). However, other investigators claim that, when given 10 min prior to irradiation [5.4 Gy (540 rads)], it protects liver, spleen, and kidneys somewhat better than MEA (173).

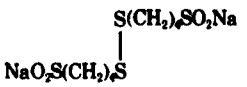


(27)

An interesting class of antiradiation compounds bearing both disulfide and butanesulfinate groups but lacking a basic amino moiety has been developed. The most active of the class are (28) [*19293-56-2*] and its disproportionation product (29) [*34915-82-7*], which is devoid of a nitrogen-containing functionality (174–175).



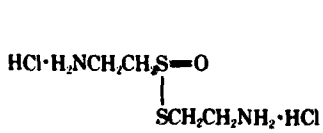
(28)



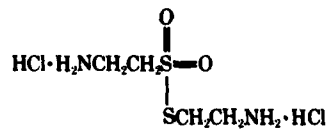
(29)

These compounds protect 93% and 73% of lethally irradiated mice at doses of 172 mg/kg and 200 mg/kg, respectively. The former also protects 100% of the mice if it is administered at a dose of 278 mg/kg po (175–176). The trisulfide corresponding to (**29**) [*56527-86-7*] protects 100% of irradiated mice when 300 mg/kg is given ip (175). At a dose of 37.5 mg/kg, the trisulfide protects 73–93% of irradiated mice when given ip (176). The main disadvantage of the sulfinates is their long-term instability and the difficulty with which pure samples are prepared.

Initially, the controlled oxidation of cystamine dihydrochloride yields 2-aminoethyl 2-aminoethanethiolsulfinate dihydrochloride (**30**) (177), and then the related thiolsulfonate [*81643-76-7*] (**31**) (178).



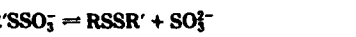
(**30**)



(**31**)

Whereas (**30**) is almost nonprotective (179), (**31**) is protective, as are its *N*-acetylated and *N*-decylated derivatives (166).

Organic Thiosulfates (Bunte Salts). In contrast to thiols, which are susceptible to air oxidation, organic thiosulfates (Bunte salts) are essentially unaffected by air. In addition, they can be solubilized by formation of their alkali salts. Furthermore, the latter react *in vitro* and *in vivo* with sulfhydryls to form mixed disulfides (180–181). A review on the chemistry and applications of Bunte salts is given in ref. 182.



Bunte salts usually have lower acute toxicity than the corresponding thiols; however, their antiradiation properties tend to be inferior to the latter, especially when they are administered orally (79,183).

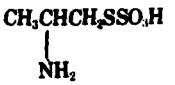
2-Aminoethanethiosulfuric acid [*2937-53-3*] (**32**) increases the survival of irradiated mice (184).

(**32**)

When administered at a dose of 150 mg/kg ip to lethally irradiated mice, (**32**) protects 73% of them (79). The same compound is effective when administered orally to mice subjected to x irradiation of 6–8 Gy (600–800 rads) for more than 6 h (185). The material, like MEA, protects against chromosomal aberrations in the bone marrow of mice exposed to x rays (186). Also, if incubated in rat tissue homogenates, (**32**) reacts rapidly and nonenzymatically with a protein sulfhydryl group to form MEA, cystamine, protein-bound MEA disulfides, and sulfite ion (181).

3-Aminopropanethiosulfuric acid [*13286-24-3*] is a less effective antiradiation agent than either its lower homologue (**32**) or MEA and protects 40% of irradiated mice at a dose of 500 mg/kg (79,187–188). 1-Aminopropane-2-thiosulfuric acid [*2403-34-1*] (**33**) and its isomeric Bunte salt 2-aminopropane-1-thiosulfuric acid [*2403-32-9*] (**34**) have been tested, but only the latter shows radioprotective activity (80% survival at a dose of 350 mg/kg) (79).

(33)



(34)

Increasing the number of methylene groups that separate the amino and thiosulfuric acid functions to 4 and above results in loss of antiradiation activity (79). Bunte salts derived from amino acids have shown limited radioprotective properties (189–190).

N-Alkylated-2-aminoethanethiosulfuric acids, of which over 100 have been synthesized, lose their water solubility and become waxlike as the chain length increases. High antiradiation activity is, nevertheless, observed from many of the poorly water-soluble compounds. 2-Methylaminoethanethiosulfuric acid [*1000-68-6*] possesses about the same activity as the parent compound in mice. When R ranges from ethyl to hexyl, derivatives (35) are nonprotective (191). However, activity returns if R = heptyl (2-heptylaminoethanethiosulfuric acid [*1191-49-7*]) and is maximized at R = decyl. The latter compound, decylaminoethanethiosulfuric acid [*3752-51-0*] (36) (WR 1607), protects 90% of irradiated mice at the low dose of 5 mg/kg (191–192).

(35)

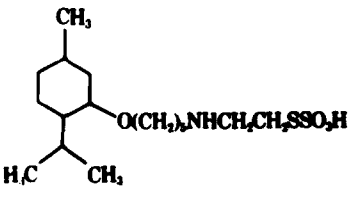
(36)

Placement of the amino function at the 2- or 3-positions of the decyl group results in the need for the greater dose of agent to maintain the same level of radioprotection. The incapacitation of rhesus monkeys that have received massive doses of radiation is prevented by prior administration of 10 mg/kg of (36) (193). The same compound also protects 50% of *Mucaca mulatta* monkeys against 8.5 Gy (850 rads) (194–195). Analogues above C_8 are not effective when administered orally.

Of a group of *N*-phenylalkylaminoethanesulfuric acids, the greatest activity is shown by *N*-(4-phenylbutyl)aminoethanethiosulfuric acid [*23464-46-2*] (37) (191). The presence of a *p*-methoxy group on the phenyl ring of (37) yields *N*-[4-(4-methoxyphenyl)butyl]aminoethanethiosulfuric acid [*21208-80-0*], which has improved activity (196).

(37)

Cyclohexyl and cyclohexenyl moieties in place of the phenyl ring in (37) also yield active compounds, ie, *N*-4-(cyclohexyl)butylaminoethanethiosulfuric acid and *N*-4-(cyclohex-3-enyl)butylaminoethanethiosulfuric acid (197). An interesting terpenelike compound is (38) (198), which affords 100% survival in mice at a dose of 15 mg/kg.



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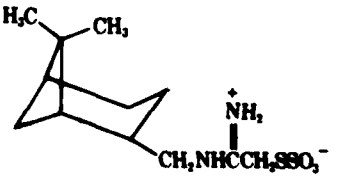
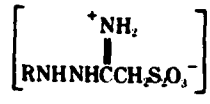


(39)

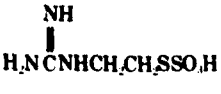
The bridging of two molecules of 2-aminoethanethiosulfuric acid by 2–6 methylene groups, as in $[HO_3SSCH_2CH_2NH(CH_2)_nNHCH_2SSO_3H]$, eliminates antiradiation activity (199). A series of *N*-heterocyclic 2-aminoethanethiosulfuric acids is essentially inactive (164).

Many Bunte salts with amidino groups have been prepared (200–203). Among them are many alkyl, cycloalkyl, cycloalkylalkyl, and aralkyl compounds that show good activity (203). Some of the most effective possess terpenoid structures, eg, (39). The substitution of an amidino group for an amino group in a series of well-known antiradiation compounds does not significantly affect the radioprotective properties of the compound (204). A small number of α-amidrazonium thiosulfates (40) show poor activity (205).



(40)

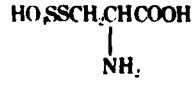
2-Guanidinoethanethiosulfuric acid [*7176-65-0*] (41) affords 80% survival in lethally irradiated mice when administered at a dose of 100 mg/kg (206–207).



(41)

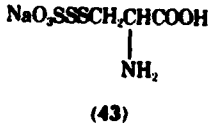
Structure modification in the guanidino group or extension of the N–S distance beyond two methylene groups results in great loss of activity.

The Bunte salt related to cysteine, ie, *S*-sulfocysteine [*1637-71-4*] (42), is weakly protective (79,208).



(42)

The related sodium cysteinethiosulfate [*7381-67-1*] (43) is protective if given 5 min before irradiation at a dose of 250 mg/kg (209–211).



(43)

Phosphorothioates. The most promising of the modified thiol groups to be incorporated into potential radioprotective agents is the phosphorothioate functionality. Compounds bearing this group do not undergo typical thiophilic displacements, to which disulfides or Bunte salts are subject, to give mixed disulfides. Phosphorothioates, however, are hydrolyzed very rapidly in the presence of acid to give the corresponding thiols and are enzymatically converted to thiol and orthophosphate by human erythrocytes, bovine brain, rat liver homogenates, and isolated acid or alkaline phosphatases (213–216).

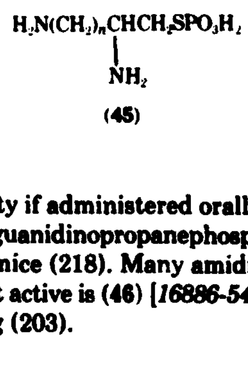
Sodium 2-aminoethanephosphorothioate [*3724-89-8*] (**44**) (sodium 2-aminoethanethiol dihydrogen phosphate, WR 638, cystaphos) was first prepared and studied in 1959 (217).

$$H_2NCH_2CH_2SPO_3HNa$$

(44)

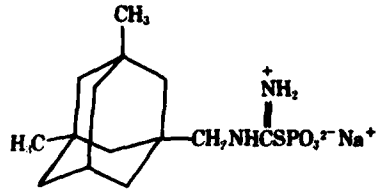
It has excellent radioprotective action [(>95% survival in lethally irradiated mice) (218)] and is superior to MEA when given orally (219). In rats, the compound exerted its maximum radioprotective action when given 60–90 min prior to irradiation (220). Its ability to protect the DNA molecule from the effects of γ radiation (221) and to work synergistically with 2-aminoethylisothiuronium bromide hydrobromide [*151-16-6*] (AET) in mice (222) has been demonstrated.

Many *N*-substituted derivatives of (**44**) are ineffective (218), the notable exceptions being the 1-adamantyl derivative and some related alicyclic compounds that have moderate activity (223). The homologue of (**44**) in which the backbone is extended to 3 carbon atoms is similarly inactive (218,224). Placement of a hydroxyl group on *C*-2 restores activity, but the resultant compound is inactive when administered orally (225). In general, placement of alkyl groups on either of the two methylenes separating the amine and phosphorothioate functions does not have detrimental effects (189–200,226–227). Linkage of 2 molecules of 2-aminoethanephosphorothioate by an *N,N'*-polymethylene chain gives good protection if either 3 or 4 methylene groups are present. Similarly constructed Bunte salts are inactive. Members of a series of *S*-2-ω-diaminoalkyl dihydrogen phosphorothioates of type (**45**) for the most part provide high antiradiation activity (89–100%) at moderately high dose levels (200–400 mg/kg) (228).



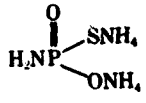
(45)

The compounds lack activity if administered orally. 2-Guanidinoethanephosphorothioate [*54978-25-5*] and 3-guanidinopropanephosphorothioate protect 97% and 80%, respectively, of irradiated mice (218). Many amidino-phosphorothioates have been synthesized. One of the most active is (**46**) [*16886-54-7*], which affords 100% protection to mice at a dose of 8 mg/kg (203).

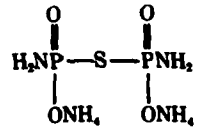


(46)

The inorganics (47) [*16886-55-8*] and (48) [*16886-55-8*] have reduction factors superior to MEA (226–227).



(47)



(48)

A particularly valuable series of antiradiation agents consists of 2-(ω-aminoalkylamino)ethyl- (49) and -propyl- (50) dihydrogen phosphorothioates (224).

$H_2N(CH_2)_nNHCH_2CH_2SPO_3H_2$ (49)

$H_2N(CH_2)_nNHCH_2CH_2CH_2SPO_3H_2$ (50)

High survivals and low toxicities characterize the former series when n = 2–6 and in the latter, when n = 2,3. The comparable Bunte salts are inactive. The excellent radioprotective ability of 2-(5-aminopentylamino)ethanephosphorothioate [*20724-76-9*] in mice exposed to x or neutron radiation has been verified (229); injury to hematopoietic organs and the gastrointestinal tract is reduced.

Probably the most effective of all antiradiation agents is 2-(3-aminopropylamino)ethanephosphorothioic acid [*41510-53-6*] (51) [WR 2721, amifostine (World Health Organization), gammaphos (USSR), YM-08310 (Japan)]. This compound protects mice, dogs, and rhesus monkeys against the effects of γ and x radiation.

$H_2NCH_2CH_2CH_2NHCH_2CH_2SPO_3H_2$

(51)

The compound protects 86% of irradiated mice at a dose of 300 mg/kg. WR 2721 promotes wound healing in irradiated rats and increases the resistance of the immune response to radiation injury (231). When administered topically, it does not provide skin protection in the mouse (232). The compound protects mouse intestine against fission neutrons (233) and x irradiation (234–235). WR 2721 is being considered for application in cancer radio- and chemotherapy.

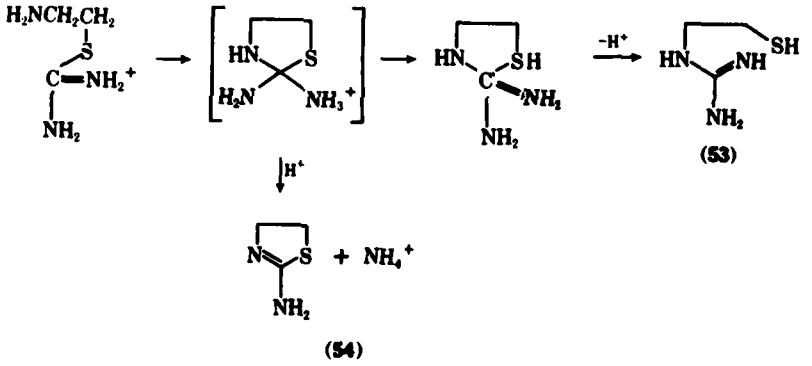
Thioureas. Thiourea [*62-56-6*] was reported initially to be nonprotective (236), as was a group of *S*-alkyl thioureas (thiopseudoureas) (237), a series of α,ω-bis(thi-

opseudoureas) (132), and *N*- and *S*-substituted thioureas (238). In a more recent paper, thiourea, methylthiourea [*2986-19-8*], ethylenethiourea [*96-45-7*], methylthiopseudourea [*2986-19-8*], and ethylthiopseudourea [*2986-20-1*] are described as radioprotectors with low toxicity in x irradiated mice (239). Favorable results have been reported more recently with a series of α,ω-bis(thiopseudoureas), in which the methylene bridges are 2–5 carbon atoms in length (240). A series of phosphorus-containing derivatives of alkylthiopseudoureas, exemplified by *S*-ethylisothiuronium ethyl phosphite [*16400-82-1*], are active when given ip to rats prior to being exposed to γ irradiation [9 Gy (900 rads)] (241).

There has been intense interest in aminoalkylthiopseudoureas and, particularly, 2-aminoethylisothiuronium bromide hydrobromide (AET) [*56-10-0*] (52).

(52)

In aqueous solution, especially near neutrality, AET undergoes a rearrangement through an intermediate diaminothiazolidine to give 2-mercaptoethylguanidine [*1190-74-5*] (53) (MEG, 2-guanidinoethanethiol).



(53)

(54)

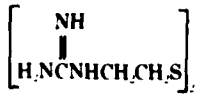
The latter is, therefore, formed by an S-to-N transfer of an amidino group. The intratransguanylation has been studied by several workers (242–245). Under fairly acidic catalysis, the tetrahedral intermediate loses ammonium ion, which results in the formation of 2-amino-2-thiazoline [*1779-81-3*] (54). This ease and multiplicity of conversions in aqueous solution has complicated the study of AET and related compounds.

2-Aminoethylisothiuronium bromide hydrobromide protects 88% of lethally irradiated mice at a dose of 250 mg/kg and is, thus, more effective than MEA on a molar basis (132). Other investigators have obtained excellent results with AET and have

noted its lack of chronic toxicity (246–250). It appears to minimize functional and genetic damage to the reproductive system (251–254). The compound is poorly tolerated by dogs (255) but seems to be nonlethal at a dose of 125 mg/kg if administered by rapid iv injection (256). The protective dose (85–100 mg/kg) is only slightly below the lethal dose.

Numerous mixtures of AET with other compounds, eg, mexamine [*66-83-1*] (257–258), dimethyl sulfoxide [*67-68-5*] (DMSO) (259–260), barbital [*57-44-3*] (261), and cysteine (262), have been studied. Aminoethylisothiuronium adenosine triphosphate (Adeturon) protects the lymphocytes in human blood against chromosomal aberrations (263).

2-Mercaptoethylguanidine (**53**) is extremely difficult to isolate, however, its oxidized form, bis(2-guanidinoethyl) disulfide [*1072-13-5*] (**55**) (GED), is readily obtained in the pure state and is stable.

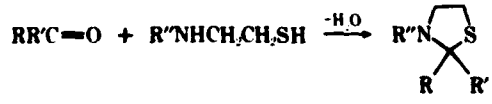


(**55**)

The latter protects the bone marrow and gastrointestinal tract of mice (56,264–265), but is more slowly adsorbed than the corresponding thiol (266–267).

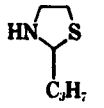
3-Aminopropylthiopseudourea bromide hydrobromide [*7072-40-4*] is superior to MEA on a molar basis but it is not as effective as AET (78). Its slower intratransguanylation has been investigated (243,268–269). 2-Aminobutylthiopseudourea dihydrobromide [*33977-39-8*] is also an active protector (270). Its optical resolution indicates that the D(−) isomer is about twice as effective as the L(+) isomer. A backbone greater than 3 carbon atoms in length eliminates radioprotective action in the AET series (271).

Thiazolines. The condensation of MEA or an *N*-substituted MEA with an aldehyde or ketone yields a thiazolidine (**56**). Numerous compounds of this type possess antiradiation activity, probably because of their ability to hydrolyze slowly *in vivo* to form their constituent aminoalkylthiols.



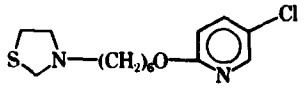
(**56**)

The correlation between radioprotection and the rate of hydrolysis as related to the substituents at the 2-positions of the heterocycle has been studied (272–273). The more active thiazolidines [eg, 2-propylthiazolidine [*24050-10-0*] (**57**), which effects 71% survival (187)], must be administered in larger doses to achieve the same order of protection as provided by the parent aminothiol.

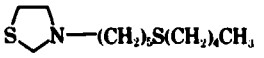


(57)

Numerous *N*-substituted thiazolidines, the alkyl chains of which have an oxy- or thiocycloalkyl, aryl, or heterocyclic group at the terminal position, have been made (198,274). One of the most active of the series is (58), which affords 93% survival to irradiated mice.



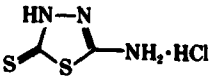
(58)



(59)

Compound (59) protects 92% if it is administered orally (275). The other active thiazolidines in animals have been correlated with their protection of irradiated human erythrocytes (276). A series of 2-phenylthiazolidines offers complete protection against one-half the LD_{50} radiation dose in mice (277–278).

2-Amino-2-thiazoline (54) effects 70% (261) and 35% (279) survival in mice, and its salts also are active (280). The 5-methyl- [*10416-80-5*] and 5-hydroxymethyl [*35525-88-3*] derivatives of (54) are active protectors of x-irradiated mice (281). The most effective of a series of 23 thiadiazoles is 2-amino-1,3,4-thiadiazole-5-thione hydrochloride [*59909-21-6*] (60), which affords 25–45% protection to x-irradiated mice at doses of 100–400 mg/kg (282).



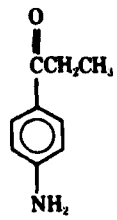
(60)

Selenium Compounds. Selenium analogues of the better known sulfur-containing antiradiation agents, eg, 2-aminoethaneselenol [*21681-94-7*], 2-aminoethaneselenosulfuric acid [*2697-60-1*] (79,283), and 2-aminoethylselenopseudourea [*1704-04-7*] (284), are toxic and nonprotective. However, in a more recent paper, it was reported that the latter compound gives significant protection to mice (285). Selenourea [*630-10-4*] protects rats subjected to 7.5 Gy (750 rads) of γ irradiation (286), whereas selenosemicarbazide [*21198-79-8*] [$H_2NNH(C{=}Se)NH_2$], at a dosage of 4 mg/kg subcutaneous, protects 50% of x-irradiated rats [6.01 Gy (601 rads)] (287). An extensive review of organoselenium compounds as potential medicinal agents is given in ref. 288.

Many inorganic selenium compounds, eg, sodium selenate [*13410-01-0*], minimise postirradiation effects of radiation in mammalian and enzyme systems (289–291).

Other Radioprotective Agents. Dimethyl sulfoxide in a dosage of 4500 mg/kg ip protects rats against 8 Gy (800 rads) (292), and is effective when applied topically to the animals' tails prior to irradiation (293–294).

Radioprotective antioxidants which have been claimed to be effective are gallic acid derivatives, eg, sodium gallate [*2053-21-6*] (295–297) and propyl gallate [*121-79-9*] (298). *p*-Aminoacetophenone [*99-92-3*] and especially *p*-aminopropiophenone [*70-69-9*] (**61**) (PAPP) have radioprotective action through their methemoglobin-inducing properties in rats and dogs (299).



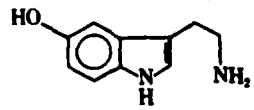
(**61**)

The latter has been used in combination with MEA and AET because it probably acts by a different mechanism than MEA and AET (300–302). A study involving a series of 27 analogues of PAPP revealed that the only consistent structural feature for activity is a free amino or hydroxylamino group (303).

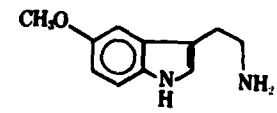
Mitotic supressive agents, eg, methyl trimethylcolchicinate [*3476-50-4*] (304) and colcemid [*477-30-5*] (305), either alone or in combination with MEA, have beneficial antiradiation properties.

Psychotropic drugs and tranquilizers, which are generally administered 3–4 h prior to irradiation, act beneficially by their hypothalmic and metabolism-depressing effects and probably are mediated through hypoxia. Compounds of varying degrees of activity are reserpine [*50-55-5*] (306–308); its *N*-oxide [*474-48-6*] (309); chloropromazine [*50-53-3*] (310–312); Sordinol [*982-24-1*], Mellerill [*50-52-2*], Truxal [*113-59-7*], and Fluanxol [*2709-56-0*] (314–315); Librium [*438-41-5*] (316); Valium [*439-14-5*] (317); Imipramine [*50-49-7*] (318–319); Trimipramine [*739-71-9*] (320); thiopental [*76-75-5*] (321); and phencyclidine [*77-10-1*] (322).

Two biogenic amines, serotonin [*50-67-9*] (**62**) (307,323–326) (5-hydroxytryptamine, 5-HT) and mexamine [*66-83-1*] (**63**) (327) (5-methoxytryptamine) are moderately active antiradiation agents in rodents when used alone.



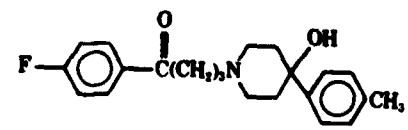
(**62**)



(**63**)

Serotonin has been studied in combination with MEA (**2**) (328) and (**44**) (329), and synergistic effects occur. Similarly, mexamine with MEA (330), cystamine (331–333), and sodium 2-aminoethanephosphorothioate (**44**) enhances the latter's protective effects. 5-Hydroxy-3-(2-methylaminoethyl)indole [*1134-01-6*] a serotonin derivative, protects irradiated mice as effectively as serotonin (335).

Luvatran [*1050-79-9*] (**64**) at 19–20 mg/kg protects irradiated mice (336).



(**64**)

Certain interferon inducers, eg, tilorone [*27591-69-1*] and *E. coli* lipopolysaccharide, have radioprotective properties (337).

8-Mercaptocaffeine derivatives bearing β-aminoethyl- and β-hydroxyethyl groups have radioprotective activity in mice that is quantitatively similar to that of cystamine (338). Other compounds and groups of compounds purported to have antiradiation properties include *N*-(dimethylamino)ethylacridones (339), prodigiosan [*82-89-3*] (340), Vitamin C [*50-81-7*] (341), orotic acid [*65-86-1*] and its derivatives (342–344), and adenosine derivatives (345) (see Vitamins, vitamin C).

Sulfur-containing polymers have been developed which could, presumably, extend the period during which the radioprotective action is in effect. Success in x-irradiated mice has been claimed for vinylpyrrolidinone formaldehyde *S*-vinyl *S*-ethylmercaptal copolymer [*35661-69-9*], vinylpyrrolidinone *N*-methacrylhomocysteine thiolactone copolymer [*34411-25-1*], and vinylpyrrolidinone acrylic acid *N*-acryl-2-methylthiazolidine copolymer [*34411-26-2*] (346). Some polymeric dithiocarbamates show antiradiation activity in mice (37) (see also Polymers containing sulfur).

Potassium iodide or iodine is used to prevent thyroid damage in humans exposed to high levels of radioiodine (^{131}I), which is attached to macromolecules, eg, an antibody or fibrinogen, during cancer therapy or diagnosis (348–349). Here, the body, particularly the thyroid gland, is saturated with nonradioactive iodine given as Lugol's solution at a dose of about 250 mg iodide per day before, during, and after administration of the radioiodinated macromolecule. Any radioiodine released from the macromolecule during metabolism or by autoradiolysis is then excreted with the excess iodide, rather than sequestered in an iodine-requiring organ, which would result in radiation damage. Thus, iodine or potassium iodide serve as radioprotective agents and the latter is, in fact, now being distributed as a chemical prophylactic for use in the event of a nuclear accident involving ^{131}I release.

Additional Uses

Cancer Treatment. In clinical radiotherapy of malignant tumors, adjacent tissue is unavoidably damaged to some extent. It is, therefore, desirable to chemically protect normal tissue from radiation injury without affecting the radiosensitivity of the tumor. Sensitizers, eg, misonidazole [*13551-87-6*], aid in achieving some selectivity (350). Modest success in the protection of normal tissue has been achieved with the use of several phosphorothioate antiradiation agents. The compounds WR 638 (44) and WR 2721 (51) are apparently less absorbed by solid tumors than by the surrounding tissue (351–356). Whereas both types of tissue actively concentrate the radioprotective agents, the deficient vascularity of the tumor or lack of some concentration mechanism places it at a competitive disadvantage (353–354). The partition of AET and MEA between normal and tumor tissues has also been examined (357). The possible utilization of mixtures of radiation sensitizers and antiradiation agents in radiotherapy is being studied (23) (see also Chemotherapeutics, antimitotic).

Numerous antiradiation agents have been investigated for cancer chemotherapy. In one effort, MEA was used to treat 11 leukemia patients but no clear benefit was observed (358). In another study, MEA showed no antileukemic activity in mice (359). The toxic side effects of several antitumor drugs in mice and rats is reduced by AET (360). Administered to mice that were given ascites cells before irradiation, AET prolonged their life although it was taken up by normal and cancerous tissues equally (361). Greater selectivity was shown by MEG (362).

To the extent that water radicals are involved in the promotion phase of carcinogenesis, use of radioprotectants may be valuable in the design of cancer-prevention regimens.

Shock Therapy. Competitive inhibition of α-adrenergic receptors can be achieved through the use of the antiradiation agents 2-(5-aminopentylamino)ethanephosphorothioic acid [*20724-76-9*] (**65**) (WR 2823), its corresponding thiol [*14653-79-3*] (WR 1729), and its corresponding disulfide tetrahydrochloride (**66**) [*31235-39-9*] (WR 149,024). The order of their ability to act as α-adrenergic blockers is the opposite order of radioprotective efficacy: WR 149,024 > WR 1729 > WR 2823.

$H_2N(CH_2)_5NHCH_2CH_2SPO_3H_2$ (**65**) $[H_2N(CH_2)_5NHCH_2CH_2S]_2$ (**66**)

WR 2823 has shown potential usefulness in the treatment of hemorrhagic (363–364) and endotoxic shock (364–365). WR 149,024 effectively attenuated anaphylactic shock in mice (366) and aided in ameliorating the effects of hemorrhagic shock in dogs (367).

Space Flight. Travel through space not only subjects humans to the possibility of exposure to ionizing radiation but also to the stress of vibration and acceleration. Studies with rodents subjected to all three factors indicate that the added trauma does not substantially affect the course of the radiation sickness (368). The extrapolation of animal data to humans regarding the use of chemical antiradiation agents during space flight has been studied (369–370) (see Space chemistry). Mixtures containing MEA are of special interest in the USSR (371).

The additional effect of radiation upon hypokinesia (immobilization) has also been studied in the USSR. In general, the radioprotective action of such agents, eg, mexamine and cystamine, is reduced in animals subjected to both types of trauma (332).

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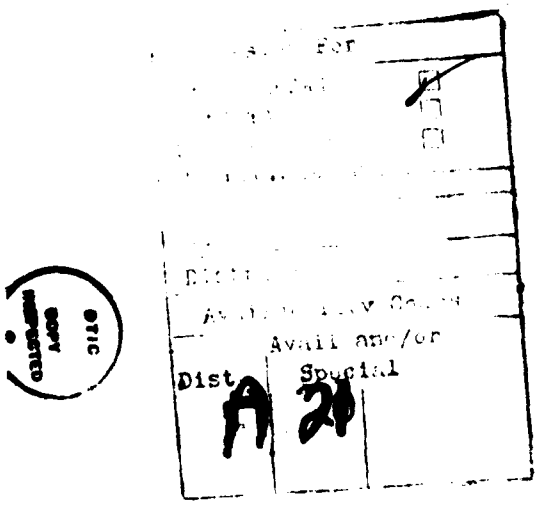

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radiation-induced injury, radical scavenging, hydrogen-transfer reactions, mixed-disulfide, hypoxia, hypothermia induction, lethal ionizing radiation, antiradiation agents, thiols, di- and trisulfides, organic thiosulfates, phosphorothioates, thioureas, selenium compounds, 2-mercaptoethylamine, anti-oxidants, mitotic-suppressive agents, psychotropic drugs, chemoprotection (contd

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The events of radiation-induced injury and death in mammals exert effects at the molecular, cellular, and organism levels. Such events can be minimized or reduced with the use of exogenous chemicals as antiradiation agents. The processes by which radiation damage is ameliorated can be explained in terms of radical scavenging, hydrogen-transfer reactions, mixed-disulfide formation, and hypoxia and hypothermia induction. Testing of a candidate agent for efficacy against lethal ionizing radiation is usually performed in mice at the maximum tolerated dose, which is administered intraperitoneally 15-30 minutes prior to

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19. cancer radio- and chemotherapy, therapy of hemorrhagic, endotoxin, anaphylactic shock, space travel.

20. radiation exposure. Survival of the treated animals for 30 days, when there is 100% mortality of the controls, indicates that the tested compound possesses radioprotective properties. Antiradiation agents fall into the following classes: thiols, di and trisulfides, organic thiosulfates, phosphorothioates, thioureas, and selenium compounds, and they tend to be modeled after 2-mercaptoethylamine. There is a smaller group consisting of antioxidants, mitotic-suppressive agents, psychotropic drugs, and biogenic amines. Several additional uses for radioprotective agents are in treatment of heavy metal poisoning, in chemoprotection during cancer radio- and chemotherapy, in the therapy of hemorrhagic, endotoxin, and anaphylactic shock, and in space travel.