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Amino acids and their derivatives as radioprotective agents

Review Article

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Summary. Numerous amino acids and their analogs are capable of protecting biological systems from the toxic effects of ionizing radiation. These radioprotective agents can be classified into two broad groups, depending upon the presence or absence of a free or potentially free sulfhydryl group. The sulfhydryl-containing compounds have been studied extensively and are thought to exert their radioprotective effects by several mechanisms, including free radical scavenging and hydrogen atom donation. Several non-sulfhydryl-containing amino acids are also being investigated for their radioprotective effects. These agents are less well known than the familiar sulfhydryl compounds, but possess very interesting protective qualities. In short, the study of amino acids and their derivatives as radioprotective agents continues to contribute to an understanding of processes involved in radiation toxicity and to offer new compounds with potential application to situations of human exposure.

Keywords: Amino acids – Radiation toxicity – Radioprotection – Thiols – Free radicals

1 Introduction

1.1 Overview

Soon after the discovery of radiation in the late nineteenth century, it was observed that this newly characterized phenomenon could cause severe and widespread damage to the human body (Walsh, 1897). Exposure risk was rapidly diminished by common sense and increased clinical diligence. However, the utility of a substance capable of protecting the body from the multi-faceted hazards of radiation exposure was immediately recognized.

The reasons for pursuing research on known and unknown radioprotective compounds are numerous and varied. Military applications were the stimulus

for the initial work in the field, with an agent capable of protecting soldiers in the nuclear battlefield the desired goal. These uncontrolled situations present numerous challenges to the designer of a radioprotector. The exact type and quality of the radiation may not be known. The dose distribution and dose rate of the radiation to the body is likely to be non-homogenous, and the radiation exposure may be accompanied by additional stress and injury. These events may occur in the face of a continuing requirement to fulfill duties that affect a large number of individuals; therefore, there must be no increased performance decrement. The radioprotector for these circumstances must be stable for extended periods of time in all types of climate conditions, be easily (preferably self-) administered, and present little toxicity of its own that would further threaten essential functions (Walker, 1988b).

The possibility of radiation exposure during an accident at a nuclear installation has taken on gargantuan proportions since the accident at the Chernobyl Nuclear Power Station in the Soviet Union on April 26, 1986. Other related problems include the potential for catastrophes during the proposed transport of nuclear waste to sites such as the Waste Isolation Pilot Project (WIPP) near Carlsbad, NM. Even the destruction of the ozone layer, which allows an increased amount of damaging solar radiation through the atmosphere, will impact the radiation received from the environment (Peak and Peak, 1989). People living near the southern tip of Chile are already experiencing the effects of ozone depletion, with a dramatic increase in the incidence of cataracts. Levels of radon (Clarke and Southwood, 1989) and other natural radiation sources (Aarkrog, 1990) in the environment may actually pose more of a risk than nuclear facilities. These examples also represent uncontrolled exposures that are accompanied by the same uncertainties as the military situations.

Other situations represent exposures from more clearly defined and monitored sources. Occupational exposure to employees at nuclear facilities (Gardner et al., 1990; Shore, 1990) or to workers involved in the clean-up and/or storage of nuclear waste material falls into this category. Radiation exposure received during prolonged space flight is also more predictable in most cases.

Another critical need in the area of radioprotection is an agent that can be used during therapeutic radiation (internal or external) of cancer (Shaw, 1990). Protection of normal tissue at the expense of tumor tissue would greatly increase the therapeutic efficacy of the radiotherapy by allowing higher levels of radiation to be employed. This represents a highly controlled situation in a health care facility, which reduces the demands on the radioprotective compound. However, significant challenges still remain. In particular, protective compounds are required that can protect against radiation-induced production of secondary tumors (Grdina et al., 1988).

Therefore, several types of radioprotective compounds are desired: (1) prophylactic (dietary) agents for individuals known to be entering high risk situations or living in a high risk environment; (2) agents administered shortly before or after a known occupational or therapeutic exposure; or (3) antidotes to an unexpected accidental exposure. It is doubtful that one agent will be able to fulfill the wide variability illustrated in this list of requirements.

1.2 Purpose and scope

While numerous physiological methods exist that may positively impact radiation-induced damage to biological systems (Phillips, 1988), the purpose of this review is to summarize information about the use of amino acids and their derivatives as radioprotectors. Further data on physiological methods of radioprotection will not be presented, except as they may relate to the radioprotective compounds being discussed. Extensive background material has also been provided in an attempt to put the discussion of radioprotective agents in a more complete and understandable framework. More detailed information is provided for the less well known amino acid radioprotectors as opposed to the more familiar agents used for this purpose. Material was incorporated from published reports up to and including 1990.

Numerous types of compounds, other than amino acids, are being investigated as radioprotective agents. These include tocopherols, selenium, ascorbate, calcium antagonists, prostaglandins and leukotrienes, histamine antagonists, vitamin A and ß-carotene, numerous biological response modifiers and growth factors, polysaccharides, steroids, herbal remedies, and deuterium oxide. These non-amino acid compounds will not be covered in this review. A discussion of proteins/enzymes that may play a role in protection against radiation toxicity also falls outside the scope of this article. Numerous reviews encompassing some of these and other topics relating to radioprotection have appeared in the literature (Patt, 1953; Bacq, 1965; Foye, 1969; Foye, 1973; Klayman and Copeland, 1975; Copeland, 1978; Harris, 1983; Goffman et al., 1990; Wardman, 1990). Several recent symposia were especially useful in preparing this review (Sutherland, 1982; Cerutti et al., 1988; Weiss and Simic, 1988).

It is assumed that some excellent work in the area of amino acids and radioprotection will fail to appear in this article due to the shear size of the data base. Apologies are extended for any unintentional errors of omission.

2 Background information

2.1 Radiation

2.1.1 Ionizing versus non-ionizing

Radiation is defined as energy propagated through a medium or the process of emitting energy in the form of particles or rays. Radiation can be divided into two categories: (1) non-ionizing, which is not capable of producing atoms or particles with a positive or negative charge; and (2) ionizing, which is capable of separating an electrically neutral atom or molecule into electrically charged components. Non-ionizing radiation is derived from heat, light, ultrasound, microwaves, television, and radio. In contrast, ionizing radiation comes from radioactive materials or radiation producing equipment such as accelerators, reactors, or X-ray machines. While the potentially deleterious effects of non-ionizing radiation are receiving more attention recently, ionizing radiation is of particular interest to the radioprotection field.

2.1.2 Types of ionizing radiation

Ionizing radiation can arise from inside the nucleus and can take on several forms. An alpha particle is a charged particle emitted from the nucleus of an atom that has a mass and charge equal in magnitude to that of a helium nucleus (two protons and two neutrons). An alpha particle has a electrical charge of plus two and is directly ionizing. It has a high density ionization path and a very short range. Alpha particles with 1 MeV of energy can produce approximately 100,000 ion pairs per centimeter of path length in air. A sheet of paper can be used to shield against alpha particles.

A beta particle is a charged particle that is emitted from the nucleus of an unstable atom and has a mass and charge equal in magnitude to that of an electron. A beta particle has an electrical charge of either plus or minus one and is also directly ionizing. It is less densely ionizing and has a longer range than an alpha particle, producing approximately 100 ion pairs per centimeter of path length in air at 1 MeV. Proper shielding materials include glass, aluminum, or clothing.

A neutron is an elementary nuclear particle that has no electrical charge and is approximately the same mass as a proton. It is emitted in certain types of nuclear reactions. A neutron is indirectly ionizing and has a high density of ionization and a longer range than alpha or beta particles. Water or polyethylene results in effective shielding from neutrons.

Gamma radiation is short wavelength electromagnetic radiation that is emitted from the nucleus of an atom. A gamma ray is a massless, chargeless packet of energy that is indirectly ionizing and has a low density of ionization; thus, it penetrates matter/tissue more deeply than alpha or beta particles. Concrete or lead is required for effective shielding.

Three kinds of ionizing radiation are non-nuclear in origin, i.e., they originate from outside the nucleus of the atom. X-rays are electromagnetic energy that are emitted when an electron moves from a higher energy orbit around the nucleus to a lower energy orbit. Except for the location of origin, X-rays are very similar to gamma rays. Bremsstrahlung is electromagnetic radiation emitted when a beta particle slows down as it moves past the nucleus of an atom. In other words, it is a secondary photon produced by the slowing of charged particles passing through matter. Low energy, but damaging, Auger electrons are often emitted after the ionization of inner atom shells during radioactive decay (Sastry and Rao, 1986).

2.1.3 Units of radiation

One of the difficulties involved in surveying the literature on the topic of radiation protection or, in fact, for any studies involving radiation, is the lack of consistency in units. The following summary is provided to facilitate understanding of the experimental details to follow.

The Curie (Ci) is the unit of activity, i.e., it describes the number of nuclear transformations per unit time. It is usually expressed as disintegrations per

minute (dpm), with 1 Ci = 2.2×10^{12} dpm. The Système International (SI) unit of activity is the Becquerel (Bq), where 1 Bq = 1 dpm.

The unit of absorbed dose is the rad (radiation absorbed dose). It is defined as the energy imparted to matter by ionizing radiation per unit mass of irradiated material at the place of interest; 1 rad = 100 ergs per gram. The SI unit of absorbed dose in the Gray (Gy), where 1 Gy = 100 rad.

The rem (Roentgen equivalent man) is the unit of dose equivalence. It is the product of the absorbed dose in rad and a "quality factor," a quantity that depends on linear energy transfer characteristics and, therefore, on the type of radiation being discussed. This measurement allows for the comparison or addition of the doses from different types of radiation for radiation protection purposes or risk assessment. The quality factor for alpha radiation is 20, for beta and gamma radiation is 1, and for neutrons is 1 to 11. The SI unit of dose equivalence is the Sievert (Sv), where 1 Sv = 100 rem.

The Roentgen (R) is used to measure exposure. Classically, it only applies to X-rays or gamma rays travelling through air and is defined as the amount of charge in a given volume of air (2.58×10^{-4} coulombs per kilogram). 1 R = 0.877 rad in air or 0.98 rad in tissue. Therefore, 1 R $\sim$ 1 rad $\sim$ 1 rem in biological systems for gamma or beta radiation.

2.2 Radiation-induced damage

2.2.1 Direct versus indirect effects

At the atomic level, the initiating event of radiation-induced damage is the ionization of atoms. This causes "direct effects" at the molecular level, where a biologically important molecule receives energy directly from incident radiation. Energy deposition on these target molecules is a random process that depends on the number of molecules present and their spatial distribution along the path of the radiation. The ionizing event can then be repaired or "fixed" by oxygen to form a lesion (see below).

Because water molecules make up about 75% of the cell, they are extremely likely to be the direct targets of ionization. The water-derived reactive intermediates then go on to damage critical targets within the cell, the so-called "indirect effect" of ionizing radiation.

2.2.2 Mechanisms of damage

The incidence of ionizing radiation on biological systems causes the production of free radicals which non-selectively effect cellular target molecules and lead to the symptoms noted. A variety of reactive free radicals are thought to be produced by this process, including hydrogen and hydroxyl free radicals, hydrated electrons, hydrogen peroxide, and superoxide anion radicals. While damage to numerous components of the cell have been demonstrated, the nucleus is the most radiosensitive component of the cell. It is well supported that the critical target molecule is DNA (especially after exposure to low-level

ionizing radiation) perhaps not because of its absolute reactivity with free radicals, but rather due to its crucial role in the cell (Greenstock, 1988). DNA can be physically broken by radiation, causing its synthesis to be slowed or stopped, and genetic material to be altered or lost. The extent of damage depends on cellular conditions, radiation dose, and the time available to effect repair of the damage.

Other sites for cellular damage include the cell membrane (Raleigh, 1988), which can be damaged at low radiation doses or ruptured at high doses. The membranes of other cellular organelles can be affected as well. In addition, protein production can be reduced or destroyed, causing disruption of cellular metabolism and/or structure.

2.2.3 Variability of response to radiation

There are a number of factors that determine the extent of the damage to a biological system caused by ionizing radiation. In regards to the radiation itself, the total absorbed dose is critical, with higher doses causing greater biological effects. The rate at which the dose is delivered to the individual is also critical when considering effects from radiation. A single large exposure (10 rem or greater) during a short period of time is defined as an acute dose and can cause immediate effects, as well as considerable long-term damage. A chronic dose is delivered over a longer period of time, with a long latent period before effects become noticeable. As discussed above, the type of radiation can dictate the level of damage. The higher the quality factor of the radiation, the greater the biological effects.

In regards to the individual receiving the exposure, the age of the person affects the level of damage, with a large degree of individual variations in sensitivity. In general, the human body becomes relatively less sensitive to ionizing radiation with increasing age. The developing embryo is the most sensitive. The area of the body exposed is also important because the extremities are less sensitive to radiation than are internal organs. In general, the larger the area that is exposed to the radiation, the greater the biological effect.

In regards to the cells being irradiated, the rate of cell division can determine the extent of damage, as can the stage of the cell cycle (Sigdestad et al., 1988). The most sensitive cells are those that divide the most frequently (intestinal cells, bone marrow, blood cells, cells that form sperm) (McCarthy and Hale, 1988). Also, the least sensitive cells are those that are the most highly specialized (brain, nerve, muscle). The conditions inside the cell are also critical to the production and extent of damage. Temperature and hydration levels can affect radiation-induced damage. The single most important aspect, however, is the level of oxygenation within the cell (Denekamp et al., 1988). Oxygen "fixes" the lesions caused by energy deposition. Hypoxia offers little oxygen for this process and allows repair mechanisms to predominate, hence the inherent radioresistance of solid tumors. The effect of oxygen on radiation damage is very important to remember when evaluating and comparing experimental data. The levels of endogenous thiols can also dictate the development of damage because these

cellular constituents have been implicated in competing with oxygen and thereby reducing the lesion formation (see below).

2.2.4 Manifestations of radiation toxicity

The basis for knowledge about the effects of radiation comes from extensive animal experiments that have been carried out for more than 40 years. Equally important is the large data base on human effects that has been compiled from atomic bomb survivors, Bikini Island residents, early radiologists and scientists, patients treated for arthritis of the spine, children treated for thymic enlargement, children exposed before birth, radium dial painters, and uranium and pitchblende miners.

At whole-body radiation doses of 100 rad, acute radiation sickness (ARS) to 50% of the exposed individuals will result. Primary symptoms of radiation sickness include nausea and vomiting, malaise and fatigue, fever, blood changes, loss of hair, infection, diarrhea, exhaustion, disorientation, and cardiovascular disruption. A radiation dose of 200 rad will produce ARS in 100% of exposed individuals. Besides these physiological decrements, performance decrements can occur within minutes near this dose of radiation (Bogo, 1988). Severe problems with increased nausea, vomiting and diarrhea appear between 200 and 400 rad, but the prognosis is still quite favorable for these individuals. The $LD_{50/30}$ (lethal dose to 50% of exposed individuals within 30 days) for acute exposure is about 400 rad. An immediate reduction in mental and physical capacity appears at a radiation dose of about 500 rad. Specific effects to the eyes are especially evident at 600 rad, with dramatically increased incidence of cataract production. If survived, 800 rad of radiation can cause permanent sterility. At 1000 rad, 99% of exposed individuals die even with treatment. Besides these general effects, there can be considerable local damage, especially to the skin (Hopewell, 1990), depending on the circumstances.

Toxicity to the blood forming organs is the first symptom of radiation exposure. This hematopoietic syndrome occurs at exposures of 300 to 900 rad and can produce death in 1 to 2 months. Gastrointestinal system effects appear second at doses above 900 rad and cause death in about 2 weeks. These derangements in intestinal function can be fatal even when the hematopoietic abnormalities are corrected by bone marrow transplantation (Geraci et al., 1988). The central nervous system is affected immediately at doses above 5,000 rad and can cause death in hours or minutes (Walker, 1988a).

Lower level exposures, such as those considered "occupational," can be characterized mainly by cataract formation, life shortening, and by increased incidence of cancer later in life (Levitt, 1989; Broerse and Dennis, 1990).

The potential effects of ionizing radiation on the fetus again depends on the type of radiation, the dose, and the dose rate. The most sensitive stage of development of the fetus is generally during the transition between undifferentiated and cellular states. In humans, this occurs between 18 and 45 days after fertilization, when pregnancy may not yet be recognized. Radiation effects to the fetus are considered negligible at <5 rad, but at acute exposures of >15 rad, growth retardation, mental retardation, malformations and death can result.

2.2.5 Methods of damage assessment

Classically, radioprotective compounds are assessed by measuring the survival of animals at 30 days after various doses of ionizing radiation. This yields critical information but does not address underlying mechanisms of protection.

More recently, techniques have been introduced that allow an investigation into the effect of ionizing radiation and radioprotective compounds on DNA itself (Kohn and Grimek-Ewig, 1973; van der Schans et al., 1988). Several specific effects on DNA have been noted including: (1) single strand breaks; (2) double strand breaks; (3) DNA-protein crosslinks; and (4) DNA base damage or deletions. The double strand break is thought to be responsible for the majority of lethality due to ionizing radiation, primarily because of repair difficulties (Painter, 1979; Radford, 1985; Ward, 1988).

Radioprotective activity is often designated as the protection factor (PF), dose modifying factor (DMF), dose reduction factor (DRF), modifying factor (MF), radioprotective factor (RF), etc. These designations are usually defined as the ratio between the radiation $LD_{50/30}$ of the protected and the unprotected animals and denote an increase in radioresistance relative to the untreated controls. A value of >2 shows good radioprotective activity; anything approaching 3 is excellent. Other biological endpoints such as DNA breakage can also be used in similar calculations. The protective coefficient of radiation (PCR) is also used periodically. Here, the survival coefficient of the "protected" mice (S), based on the number of surviving animals on each day, is divided by S for the control groups. In studies involving differences in oxygen tension, the oxygen enhancement ratio (OER) is often calculated, which relates to the amount of oxygen needed to achieve half-maximum radiosensitivity in the presence of added protective agents.

3 Radioprotective agents

3.1 Sulfhydryl

Thiol radioprotective agents appear to function by a combination of different mechanisms. Sulfhydryl compounds can effectively compete with oxygen for the free radicals produced by ionizing radiation. This classic model of "oxygen fixation competition" explains the reduction in oxidative chemical changes subsequently produced by the free radicals (Alper and Howard-Flanders, 1956; Tamba, 1989). Logically, the protection afforded by these sulfhydryl compounds decreases along with the concentration of oxygen in the system. Therefore, the protective activity is decreased in hypoxia, a common characteristic of tumors. Sulfhydryl compounds can also repair damaged target molecules by efficiently donating hydrogen atoms. Their effects on intracellular free thiols through thiol/disulfide exchange may also be important (Bacq and Alexander, 1964).

The indirect effects of these compounds are possibly even more intriguing, with the regulation of oxygen levels at the site receiving the most attention. Indeed, some investigators believe that at least some of the sulfhydryl radioprotective agents exert their most profound effects by altering the availability of oxygen to the system (Durand and Olive, 1989). The ready oxidation of thiols,

especially in the presence of heavy metals, may also play a role (Ziegler et al., 1983).

The most active sulfhydryl radioprotective compounds are in fact aminothiols in which the two functional groups are no more than three carbon atoms apart. The sulfhydryl can either be free or potentially free after enzymatic or non-enzymatic processing.

3.1.1 Amino acids

3.1.1.1 Cysteine

$$HSCH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCOOH$$

Patt et al. (1949) first demonstrated that the sulfhydryl amino acid, L-cysteine, could protect rats against radiation-induced hematopoietic death. This set of experiments marked the birth of the field of radioprotection. While cysteine proved not to be the agent of choice mainly due to its toxicity at radioprotective doses, it continues to be the subject of considerable study. In particular, cysteine showed dramatic protection against chromosome aberrations in human lymphocytes induced by up to 7 Gy (Virsik and Harder, 1982). In studies with isolated DNA, cysteine did demonstrate protective abilities by intervening in free radical damage processes, but it was not able to restore sites that were damaged by the radicals (Lafleur et al., 1980).

While cysteine may directly intervene in radiation-induced free radical damage, it also is a critical precursor of glutathione (GSH) which may also account for its radioprotective effects.

3.1.1.2 Cysteamine

$$HSCH_2CH_2NH_2$$

Soon after cysteine's radioprotective qualities were outlined, Bacq and coworkers (1951) showed that its decarboxylated product, cysteamine, possessed even greater activity against ionizing radiation. Unfortunately, cysteamine also exhibits toxicity at radioprotective doses which severely limits its utility.

Cysteamine has been shown to decrease the incidence of DNA single-strand breaks in irradiated cells (Lohman et al., 1970). In addition, cysteamine also appeared to be able to alter the entire spectrum of lesions on cellular DNA to different extents (Radford, 1986). Significant protection against intestinal metaplasia was demonstrated in Sprague-Dawley rats receiving 20 Gy of X-irradiation to the abdomen (Watanabe et al., 1988). Protection of isolated, single-strand DNA by cysteamine appears to be due to a large extend to repair of the damaged sites, in contrast to results obtained with L-cysteine (Lafleur et al., 1980). The additional capacity for repair is thought to be due to hydrogen atom transfer to damaged sugar residues; however, this hypothesis does not adequately explain cysteamine's superior performance. Cysteamine also exhibited a dose-dependent ability to elevate cellular GSH (Révész and Modig, 1965; Djurhuus et al., 1990).

The protective effects of cysteamine have also been established against α-particles (Barendsen and Walter, 1964), high energy neutrons (Antoku, 1975), and helium ions (Bird, 1980), but the level of protection was always lower than that against X- or gamma-radiation. Recently, protection against Auger electrons, which possess low energy but high potential for producing biological damage, was also demonstrated (Rao et al., 1990).

A series of 2-phenylthiazolidine derivatives of cysteamine were prepared and tested as radioprotective compounds (Terol et al., 1978a; Terol et al., 1978b). Several, especially the dimethylated catechol analog, showed powerful activity even at relatively low doses (one-quarter the LD_{50}). No further information is available about these interesting derivatives.

Other thiazolidine derivatives of cysteamine have been prepared from alkyl aldehydes and ketones (Kaluszyner et al., 1961). These derivatives possessed equal radioprotective activity to cysteamine itself when tested in mice receiving 725 rad total body radiation. Toxicity information was unreported, however.

3.1.1.3 Walter Reed compounds

$$NH_2(CH_2)_3NHCH_2CH_2SPO_3H_2$$

WR-2721

During the 1950s the United States Army initiated the Antiradiation Drug Development Program, an extensive set of studies aimed at developing a radioprotective compound for use in combat conditions during a nuclear war. This effort led to the synthesis and evaluation of some 4400 compounds (Sweeney, 1979). The vast majority of these studies was carried at the Walter Reed Army Hospital, and the compounds are known as the Walter Reed or WR compounds.

The lead compound for these efforts was cysteamine, which was the best radioprotector known but which possessed unacceptable toxicity. By far the most successful agents to emerge from the Walter Reed studies were phosphorothioate derivatives of the aminothiol, especially *S*-2-(3-aminopropylamino)ethylphosphorothioic acid, better known as WR-2721 or ethiofos. It is widely supported that WR-2721 is a prodrug form of the free thiol compound, WR-1065, which is the active radioprotective agent (Mori et al., 1983). Interestingly, levels of alkaline phosphatase, the enzyme thought to be responsible for activation of the prodrug, do not appear to correlate with radioprotective activity (Rasey et al., 1988).

WR-2721 and WR-1065 possess significantly less toxicity than does cysteamine, but the side effects of the compounds are still noteworthy (Landauer et al., 1987, 1988; Vaughan et al., 1989; Mahaney, 1990). WR-2721's popularity was dramatically elevated when it was noted that the drug was able to protect normal tissue at the expense of tumor tissue (Yuhas and Storer, 1969) although some controversy still exists about this point. The differential protection is most likely due to differences in blood flow between tumor and normal tissue, the drug's action in hypoxic conditions, and its active concentration by normal tissues (Yuhas, 1970).

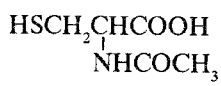
The radioprotective qualities of WR-2721 have been demonstrated in mice, dogs, and monkeys against both X- and gamma irradiation; protection against neutrons has also been seen in mice. A DRF of 3.4 has been observed in the immune system under certain conditions, the largest protective effect demonstrated to date (Yuhas et al., 1980). This compound is capable of protecting the rapidly damaged tissues of the intestine and the bone marrow, shows lesser activity in kidney and lung, and is inactive in the brain.

The phosphorothioate derivatives of cysteamine are thought to function by the accepted mechanisms of the thiol radioprotectors, namely, by free radical scavenging, induction of hypoxia, or repair of target molecules. It appears likely that the actual mechanism of action of this class of radioprotectors is much more complex than originally hypothesized (Murray et al., 1988). Indeed, recent studies (Issels and Nagele, 1989; Uma Devi and Prasanna, 1990) have indicated that WR-2721 elevates blood GSH, which, as in the case of cysteamine and cysteine, may play an important role in the action of the phosphorothioate.

While WR-2721 and WR-1065 have received the most attention, several other Walter Reed compounds have been studied extensively. The terminal *N*-methylated derivatives of WR-2721 and WR-1065, namely WR-3689 and WR-255591, respectively, gave protection against DNA damage from gamma radiation (Murray et al., 1988) and fast neutrons (vanAnkeren et al., 1989). WR-3689 is tolerated better than WR-2721, especially after oral administration. WR-77913, 3-amino-2-hydroxypropyl phosphorothioate, along with WR-2721, was able to protect against some deleterious effects of photodynamic therapy to the skin and the eye (Dillon et al., 1988). Again, this derivative was far better tolerated in mice and dogs than WR-2721.

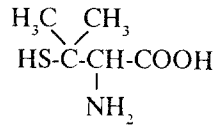
A novel set of bifunctional derivatives of WR-2721 and *N*,*N*′-bis-(3-aminopropyl)cystamine (WR-33278) have recently been synthesized by attaching an acridine or quinoline moiety to the terminal amine (Demonchaux et al., 1989). These analogs were designed to localize at DNA because of the high affinity of the heterocycles for the macromolecule. While biological data was not reported, the concept is an interesting one. It must be kept in mind, however, that aminopropylcystamine, a likely metabolite of these derivatives, is a potent inactivator of gamma-glutamylcysteine synthetase, the rate-limiting enzyme of GSH biosynthesis (Schor et al., 1990).

3.1.1.4 N-Acetyl-L-cysteine



N-Acetyl-L-cysteine (NAC) was shown to possess the least amount of behavioral toxicity of several sulfhydryl radioprotective agents. Unfortunately its protective effects against 13 Gy of whole body gamma rays to mice was poor (Landauer et al., 1988). Topical NAC showed no protection to the skin of rats exposed to gamma radiation (Verhey and Sedlacek, 1983). In contrast, studies in humans showed that NAC did protect the skin and seemed to speed up the healing process (Kim et al., 1983).

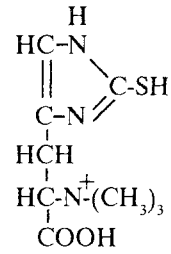
3.1.1.5 D-Penicillamine



D-Penicillamine (β,β-dimethyl-D-cysteine) is a known antagonist of collagen formation and has been investigated by Ward and others (1980) as an agent capable of delaying the development of pulmonary fibrosis in animals exposed to radiation. HA(ICR)f mice were exposed to 500–1000 rad of gamma rays and received 1, 10 or 100 mg penicillamine per mouse at varying times before and after whole-body irradiation; the animals were monitored for 30-day survival. The highest dose of penicillamine corresponded to 3000 mg/kg and was toxic to 5.5% of the animals injected. Those tolerating the dose, however, showed significantly lower radiation-induced mortality at 30 days, even after exposures of 900 rad. The protective effects were slightly less than those seen after a dose of 40 mg per mouse of L-cysteine, which produced drug-related deaths in 1.2% of the animals injected.

Continued work has demonstrated that D-penicillamine (10 mg per mouse) significantly reduced radiation-induced hydroxyproline accumulation in rat lung after 25 Gy of gamma radiation (Ward et al., 1983). This end point reflects the amount of collagen accumulation and, therefore, the extent of fibrotic disease caused by the radiation treatments. Hydroxyproline data must be interpreted with caution, however, because numerous pulmonary proteins contain significant levels of the substance. The effects were maintained for up to 12 months after irradiation. Similar doses of D-penicillamine were also shown to reduce radiation-induced injury in the endothelial tissue of the rat lung after 25 Gy of gamma radiation (Ward et al., 1984).

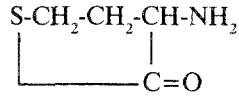
3.1.1.6 Ergothioneine



Hartman and coworkers (1988) set out to investigate some components prevalent in certain biological niches as radioprotective agents. Ergothioneine (2-thiol-L-histidine betaine) occurs in high concentrations in some fungi and apparently collects in mammals after consumption, where it can reach millimolar levels in certain tissues (Melville, 1958). Ergothioneine has been shown to inhibit lipid peroxide formation mainly by protecting against H_2O_2 formation. Ergothioneine showed good radioprotective capabilities when tested against bacteriophage inactivation at low levels (0.1 mM). It is thought to function as a thiol protective agent but may also possess some properties of thiones in solution,

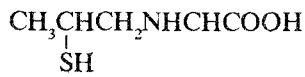
which may also react with peroxides and hydroxyl free radicals (Halliwell and Gutteridge, 1986).

3.1.1.7 L-Homocysteine thiolactone



L-Homocysteine thiolactone is of particular interest as a radioprotective compound because it is much more lipophilic than other known protective agents and may find utility as a brain protector. Biodistribution studies with the radiolabeled compound showed that membrane transport should not limit its uptake in brain. However, the actual brain levels of the compound were quite low probably due to hydrolysis to homocysteine, the actual radioprotector, which is much more hydrophilic (Grunbaum et al., 1990). Langendorff and Koch (1958) first studied the lactone as a radioprotector. In their studies, a dose of 14 mg/mouse or 100 mg/rat of L-homocysteine thiolactone showed excellent protection against up to 1150 rad of whole body gamma radiation. The *N*-acetylated derivative showed comparable protection in the same test systems. However, doses in this range have been reported to be acutely toxic to mice, producing up to 90% mortality due to a complex collection of responses (McCully and Vezeridis, 1989).

3.1.1.8 N-2-Mercaptopropionyl glycine

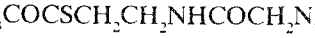


N-2-Mercaptopropionyl glycine (MPG) is unique among the thiol radioprotective agents in that its optimal protective dose is well below its toxic dose.

In *in vitro* studies, MPG protected erythrocytes from the damaging effects of 80–400 Gy of gamma radiation in a dose-dependent fashion (Ayene et al., 1988). Inhibition of lipid peroxidation was demonstrated in these studies. However, some sensitization to the effects of radiation by MPG was also noted, confirming previous reports (Ayene and Srivastava, 1985). MPG has also been useful in *in vivo* studies especially when co-administered with 5-hydroxytryptophan (see below, Ghose et al., 1983) and WR-2721 (Uma Devi and Prasanna, 1990; Bisht et al., 1990).

3.1.2 Dipeptides

3.1.2.1 S-Acetyl-N-glycyl cysteamine

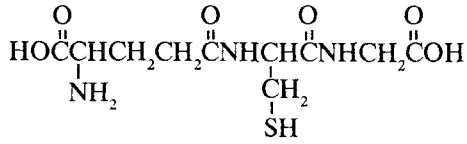


Oiry and coworkers (1986) studied a series of dipeptide analogs of cysteamine and cystamine that also featured an acetyl protecting group for the thiol function. *S*-Acetyl-*N*-glycyl cysteamine (AGC) showed the greatest protective activ-

ity in BALB/C mice receiving about 9 Gy of whole body gamma radiation (RF = 1.4). While this reduction factor is lower than that achieved with WR-2721 (RF = 2.5) in the same system, the pseudo-dipeptide appeared to be tolerated better by the experimental animals (Lespinasse et al., 1985). Metabolism studies confirmed that AGC is a prodrug of cysteamine which is liberated after enzymatic deacetylation and hydrolysis of the amide linkage (Maurizis et al., 1988). AGC, like WR-2721, exhibited preferential radioprotection towards normal tissue at the expense of tumor tissue. These differential effects are thought to be attributed to not only to poorer uptake of the protector in tumor cells, but also to the tumor's reduced capacity to deacetylate and hydrolyze the prodrug (Maurizis et al., 1989).

3.1.3 Tripeptides

3.1.3.1 Glutathione



Glutathione (GSH) was among the first compounds found to possess radioprotective activity. In 1949, inclusion of GSH in solutions of enzymes was shown to protect the proteins against radiation-induced damage (Barron et al., 1949). Since that time, thousands of studies have been conducted on GSH in an attempt to unravel its role in the radiation response.

It is widely accepted that even large variations in GSH content do not seem to affect the sensitivity of aerobic or anoxic systems to radiation. However, it is equally clear that GSH can, in fact, exert profound effects under conditions of intermediate oxygen tensions. The majority of studies involving GSH and radiation response have been conducted by using depletors of the tripeptide or inhibitors of its biosynthesis (Harris, 1983; Kinsella et al., 1986; Kramer et al., 1989; Baker and Hagner, 1990; Den Boer et al., 1990) and measuring radiosensitization. Clearly the non-specificity of action of these agents does not allow for the unambiguous interpretation of results in most cases. The development of cell lines genetically deficient in GSH-producing capacity has simplified this approach significantly and has confirmed that GSH plays a large role in the cellular response to radiation (Révész and Malaise, 1983). GSH is not only thought to produce protection by its efficiency as a hydrogen atom donor, but also to function in repair of radiation-induced damage by serving as a cofactor in crucial enzymatic reactions (Bump and Brown, 1990). GSH may also play a role in radioprotection by serving as a cofactor for enzymes such as GSH peroxidase which can detoxify organoperoxides formed by ionizing radiation.

More recently, agents that can augment GSH concentration have been studied for their ability to enhance radioprotection. Several studies have demonstrated that GSH itself can protect against radiation-induced damage in numerous systems, although GSH is not effectively transported across the cell membrane. To avoid this detriment in delivery, prodrugs of L-cysteine, such as

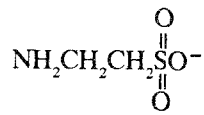
2-oxothiazolidine-4-carboxylic acid (OTZ) (Russo et al., 1985), as well as esters of GSH (Wellner et al., 1984; Vos and Roos-Verhey, 1988) have been used successfully in certain *in vitro* studies.

While GSH precursors or derivatives have exhibited potential as exogenously administered radioprotective compounds, they are less active than the aminothiols such as cysteamine. This may be due to the relative efficiencies in hydrogen atom donation (Held et al., 1984). Because of its utility in enzymatic processes, however, GSH may be an important component of a radioprotection regimen.

3.2 Non-Sulfhydryl

3.2.1 Amino acids

3.2.1.1 Taurine



The interest in taurine (2-aminoethanesulfonic acid) and its relation to radiation responses arose when it was observed that whole-body irradiation caused dramatic changes in urinary taurine excretion (Kay et al., 1957; Abe et al., 1968). Studies conducted in mice that received 690 R total body X-rays were characterized by an initial spike of taurine in the urine at day 1 after irradiation, followed by a rapid return to baseline excretion levels. At about day 11 after irradiation, however, urinary taurine began another rise, albeit more gradual, which precisely paralleled the mortality rate to the test animals. This taurine excretion profile was considered so characteristic that an attempt was made to use it for early diagnosis of radiation sickness.

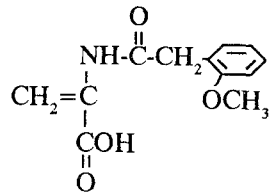
The change in taurine excretion was linked to the process of radiation injury. Studies by Langendorff and coworkers (1961) determined that taurine excretion was diminished by pretreatment of the animal with radioprotective compounds. Abe et al. (1968) took the studies a step further and examined whether taurine itself possessed radioprotective capabilities. Indeed, post-irradiation administration of taurine increased the survival of mice exposed to high doses of total body radiation. Protection was not seen, however, when taurine was given before irradiation. Taurine, therefore, was the first compound seen to exert radioprotective effects when administered after the radiation exposure. Protection was demonstrated with single doses of taurine given on days 3–9 as well as with a daily dose on each of days 3 through 8 after irradiation. Perhaps the greatest level of protection was seen when taurine was given on the fourth day after irradiation, when the urinary taurine excretion was at its lowest. Taurine, on the other hand, did little to prevent loss of white blood cells after irradiation, but did allow recovery of normal white blood cell counts much faster than untreated mice (18 days *versus* $\gg$28 days, respectively).

It has been speculated that the urinary taurine may originate from leukocytes and/or thrombocytes, which possess levels of the compound several hundred

times higher than plasma (Soupart, 1962). It remains unclear, however, whether radiation-induced damage to these cells causes release of taurine, or whether radiation-induced release of taurine causes damage to the cells. In any case, post-irradiation administration of taurine may allow repair to these critical cells damaged during radiation exposure.

In contrast to the *in vivo* results, recent work with taurine resulted in little if any protection when tested against the inactivation of bacteriophages by gamma irradiation even at 1 mM concentrations (Hartman et al., 1988).

3.2.1.2 N-Acyl dehydroalanines

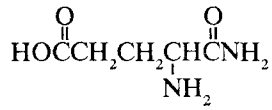


AD-20

N-Acyl dehydroalanines, exemplified by *ortho*-methoxyphenylacetyl dehydroalanine (AD-20), are a new class of radioprotective compounds designed as free radical scavengers (Praet et al., 1988; Buc-Calderon et al., 1989a; Buc-Calderon and Roberfroid, 1989). They possess a "capto-dative" olefin that can form stabilized free radical adducts and thereby reduce the reactivity of radiation-generated species, especially superoxide anion radical and hydroxyl radical (Buc-Calderon and Roberfroid, 1988). If radical attack occurs at the carbon-carbon double bond of AD-20, the resulting adduct is stabilized by the presence of both an electron-withdrawing and -donating group on the same carbon (the capto-dative effect) (Viehe et al., 1985). Alternatively, hydrogen atom abstraction could occur from the methylene carbon producing a radical that is stabilized by the aromatic ring and the carbonyl group. Most often, these stabilized species eventually dimerize to yield innocuous products.

Radioprotection studies were carried out by administering AD-20 (500 mg/kg, ip) to NMRI mice 15 minutes prior to whole-body irradiation with 700 rad of X-rays (Buc-Calderon et al., 1989a). Control animals exhibited a mean survival time of 15.2 days, compared to 23.8 days for AD-20 treated mice. The radioprotection achieved by AD-20 was of the same order of magnitude as that observed with an equimolar amount of WR-2721 in the same test system (26.7 days). An increase in life span over controls was observed in AD-20 treated animals receiving up to 800 rad of X-rays.

3.2.1.3 Glutamine



As described earlier, damage to the small intestine is a major problem associated with radiation exposure. Glutamine has been recognized as the principal fuel

utilized by the intestinal mucosa (Windmeuller, 1982) and as an important component for the maintenance and development of this critical tissue, especially after damaging events. Indeed, Baskerville et al. (1980) demonstrated the development of mucosal ulceration by infusing glutaminase and thereby reducing blood glutamine levels.

Klimberg et al. (1990b) hypothesized that providing elevated dietary levels of glutamine would protect against the potent toxicity of ionizing radiation to the intestinal tract. Their studies utilized Sprague-Dawley rats, which were supplied with a glutamine-enriched (0.66%) or glutamine-free (0%) liquid diet. Glycine was added to the glutamine-free solution such that 30% of the nitrogen was supplied by the added amino acids. Otherwise, the diets were identical.

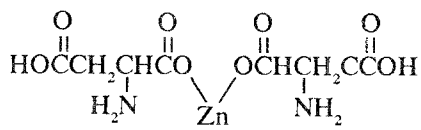
After four days on the special diet, the rats were exposed to 1000 cGY of X-irradiation to the abdomen (LD_{50} dose at day 8 to 10), with the remainder of the body shielded. All animals received glutamine-free diets for four days after the radiation treatment, and then were sacrificed for evaluation.

Interestingly, glutamine levels in arterial blood samples did not vary significantly between the two treatment groups. Also, extraction of glutamine by the gut was unchanged. The jejunal mucosal weight was significantly decreased in the animals on the glutamine-free diet, but the amount of protein and DNA in tissue samples was unaffected by the variation in diet. However, dramatic improvements were seen in rats fed the glutamine-enriched diet when the villous number per centimeter, the villous height, and the number of mitoses per crypt were compared, suggesting a more rapid turnover of the gut epithelial tissue and, perhaps, more rapid repair of the damaged cells. Also, the presence of mucosal ulcerations in all but one of the glutamine-free animals was confirmed by scanning electron microscopy. Improvement in these mucosal morphometric parameters was also demonstrated by providing the glutamine-enriched diet for four days *after* irradiation.

In contrast, more recent work from the same research group (Klimberg et al., 1990a) resulted in statistically significant differences in arterial glutamine levels in rats treated for 8 days post-irradiation with a diet containing 3% glutamine as the single amino acid nutrient. Gut glutamine extraction was also elevated in the treated population. In general, survival was again greatly improved in the animals receiving the glutamine-enriched diet.

While the mechanism of glutamine's radioprotective effects remains unclear, an increased transport of the amino acid may account for the beneficial effects by increasing the organ's capacity for repair. Greater ability to support mucosal proliferation may be a leading factor. It should be kept in mind, however, that other factors contribute to the toxicity of radiation to the bowel, namely later reactions involving fibrosis, etc., that are separate from mucosal injury.

3.2.1.4 Zinc aspartate



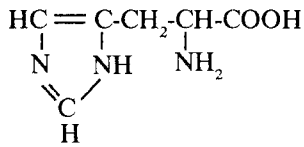
Some very interesting studies commenced in the mid 1980s investigating the effects of various zinc salts on radiation-induced toxicity in mice. Floersheim and Floersheim (1986) compared zinc chloride ($ZnCl_2$), zinc sulphate (as $ZnSO_4 \cdot 7H_2O$), and zinc aspartate (as zinc-*bis*(DL-aspartate)) as protectants against lethal doses of gamma rays in C3H mice.

Zinc aspartate showed the best protection, with significant activity even up to 13 Gy of total body radiation. (The $LD_{50/30}$ for controls was 8 Gy.) Zinc chloride exhibited a limited amount of protection, which was about three- to four-fold less than the aspartate salt. Zinc sulphate was essentially inactive. Cu-DL-aspartate and Na-DL-aspartate were also ineffective, illustrating the special qualities of zinc aspartate.

Extraordinary protection was observed when zinc aspartate was administered in conjunction with cysteamine. Enhanced survival of treated animals was shown to occur after up to 18 Gy of total body radiation, levels far above those achieved with the "best" radioprotectors known to date. Protection appeared to occur in part by reducing the levels of thymocyte depression (Floersheim and Bieri, 1990).

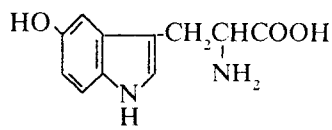
In related studies, zinc aspartate was shown to spare the bone marrow, the tissue first destroyed by radiation. However, this protection did not significantly compromise the therapeutic utility of radiation against four human tumor xenografts. In contrast, the aminothiol radioprotectors, cysteamine and WR-2721, did provide slight protection to the tumor tissue in some experiments (Floersheim et al., 1988).

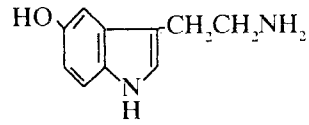
3.2.1.5 L-Histidine



The bacteriophage system was also used to evaluate the radioprotective effects of L-histidine, an amino acid prevalent in fish muscle. Histidine has been shown to scavenge singlet oxygen and possibly hydroxyl radicals (Dahl et al., 1988). At concentrations of 1 mM, histidine reduced the lethality and single-strand breaks in bacteriophage DNA exposed to X-rays, although lower doses were somewhat effective. However, at much lower concentrations (0.01 and 0.001 mM), histidine appeared to actually cause sensitization to radiation-induced inactivation of the bacteriophage. The sensitization was explained by the trapping of H_2O_2 in the form of histidylperoxide, followed by the delivery of the peroxide to the phage surface (Hartman et al., 1988).

3.2.1.6 5-Hydroxytryptophan and 5-hydroxytryptamine





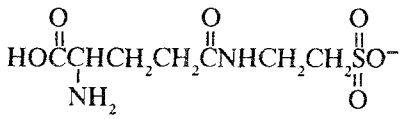
When 5-hydroxytryptophan (5-HTP) (100 or 200 mg/kg) was administered 30 minutes prior to 10.5 Gy total body radiation to mice, 30-day survival increased from zero to 10% and 68.5%, respectively (Ghose et al., 1983). To study possible augmentation effects in conjunction with thiol radioprotectors, 100 mg 5-HTP was given along with suboptimal doses of cysteine, cysteamine, cystamine, and MPG (20 mg/kg). In all cases, protection was dramatically increased over that of the individual components at the doses employed, with the greatest protection seen with 5-HTP and MPG. Similar combinations also showed radioprotection against 12.5 Gy. Evaluation of the absolute utility of the combination regimen is difficult because the dose of radioprotector did not correspond in any way to its optimum dose. In addition, the combination studies were apparently conducted by co-dissolving the desired agents in the same solution, although this fact is not apparent in the methods. Therefore, it is impossible to discern whether the agents themselves are exerting the effects in concert of whether a new entity was produced in solution prior to administration.

Other investigators (Basu et al., 1987) confirmed the radioprotective effects to peripheral blood cells of a combination of suboptimal doses of 5-HTP and thiol protective agents. Protective effects were noted at both 4 and 10 Gy total body gamma radiation to Swiss mice. An identical treatment protocol also protected Sprague Dawley rats from radiation-induced alterations in testicular activity after 8 Gy whole body radiation (Srinivasan et al., 1989).

5-Hydroxytryptamine (5-HT) has shown radioprotective effects that appear to correlate with induction with bone marrow hypoxia (Allalunis-Turner et al., 1989; Allalunis-Turner, 1990).

3.2.2 Dipeptides

3.2.2.1 Glutaurine



Glutaurine (*gamma*-L-glutamyl-taurine) was isolated from parathyroid extract and fully characterized by Feuer and coworkers in 1978. Glutaurine appeared to be practically atoxic and was considered an endogenous protective compound. Because parathyroid extract had been shown to prolong the survival of mice exposed to irradiation (Feuer and Ormai, 1978) and because of taurine's radiation protective effects, Feuer decided to investigate glutaurine's effects in radiation injury (Feuer and Benkó, 1981).

CFBL mice, pretreated with 10 μg/kg glutaurine for 4 days prior to 7.5 to 9.0 Gy of ^{60}Co irradiation, showed small but significant protection. More pronounced effects were observed in animals receiving a total of 10 Gy over an extended exposure time. Similar levels of protection were seen in animals treated with glutaurine for 4 days after irradiation.

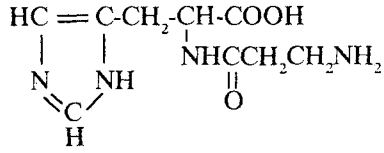
Glutaurine was also tested in combination with cysteine (100 mg/kg), cysteamine (150 mg/kg), or cystamine (150 mg/kg). In all cases, the combination

therapy was very effective in protecting against even an LD_{100} dose of radiation. The levels of aminothiols utilized was much lower than their toxic levels, allowing protection without side effects.

Feuer speculated that the most probable mechanism for the protective effect of glutaurine and its derivatives was an immunoregulatory or immunostimulatory one. It is known that glutaurine can activate macrophages and thymocytes (Feuer et al., 1978, 1979) and facilitate mast cell degranulation (Feuer et al., 1980).

While the protective effects of glutaurine are not as dramatic as the better known aminothiol compounds, it possesses a much improved therapeutic index and is active when administered after irradiation. These factors suggest that glutaurine might be quite useful in radiation protection. However, no information after the 1981 paper is available on this very interesting compound.

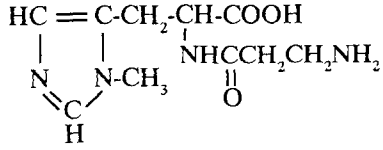
3.2.2.2 Carnosine



As discussed for ergothioneine and histidine above, carnosine (*N*-β-alanyl-L-histidine) was investigated as a protective compound because it occurs in certain biological systems, particularly the striated muscles of mammals, in concentrations up to 40 mM. Previous reports pointed to carnosine's ability to reduce lipid peroxidation, maintain mitochondrial function, and reduce muscle fatigue (Dupin et al., 1984). Hartman and coworkers (1988) speculated that carnosine may function as a defense mechanism against free radical damage.

Carnosine was tested as a radiation protective compound in the bacteriophage system also utilized for the study of ergothioneine and histidine. Dose-dependent protection was observed with a carnosine concentration as low as 0.1 mM (Hartman et al., 1988).

3.2.2.3 Anserine



Anserine (*N*-β-alanyl-*N*-l-methyl-L-histidine), a methylated derivative of carnosine, offered good protection in the bacteriophage evaluation system, but required higher concentrations (1 mM) than did carnosine (Hartman et al., 1988).

4 Future considerations

The field of radioprotection continues to offer distinct challenges. As yet, no compound fulfills even the least strenuous set of requirements. Clearly, continued study of new chemical entities is not precluded. Directly coupled with the synthesis of new agents is the growing understanding of the processes at the molecular and cellular level. Ultimately the two paths will converge.

It is also clear that amino acids and their derivatives offer numerous compounds that may be useful for radioprotection. In general, a consideration of the absorption and distribution of radioprotectors in tumor and normal tissue is critical. Continued work on improved delivery methods for these agents is called for. Hydrophilic agents appear to offer the greatest likelihood of low toxicity and differential radioprotection (Brown et al., 1988). Transdermal delivery using permeation-enhancing vehicles also holds promise (Lamperti et al., 1990; Sodicoff et al., 1990). In the area of thiol-containing protectors, a masked sulfhydryl appears to be the best route to agents with lower toxicity. An efficient mechanism for liberation of the required free sulfhydryl group is then necessitated.

Perhaps the greatest advances have been made in the use of combinations of radioprotective agents. A synergistic effect is often observed in these treatment regimens, which dramatically reduces toxicity issues encountered with higher doses of the separate drugs.

A decidedly fascinating use of these compounds is their activity as protective agents against the toxicities produced by common chemotherapeutic agents as well as against radiation. Some of these anticancer drugs are considered "radiomimetic" due to their mechanisms of action, but others are not. The *N*-acyl dehydroalanines have been shown to protect against the cardiotoxicity of daunorubicin and doxorubicin (Buc-Calderon et al., 1987, 1989b, 1990; Praet et al., 1988). Protection against cyclophosphamide's urotoxicity has been demonstrated by prodrugs of L-cysteine (Roberts et al., 1990). WR-2721 has been entered in clinical trials as a protective agent against cyclophosphamide, *cis*-platinum, and nitrogen mustard (Yuhas and Culo, 1980; Glover et al., 1986, 1988; Mahaney, 1990). Several related examples have also been reported (Nagy and Grdina, 1986; Nagy et al., 1986).

It appears inevitable that the field of amino acids and their derivatives as radioprotective agents will ultimately yield some compounds for clinical use that will greatly facilitate the management of cancer.

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