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***Invited review***

# Treatment of radiation-induced normal tissue lesions

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## INTRODUCTION

Normal tissue damage is the most important limiting factor in radiotherapy. It must be possible, at least theoretically, to eradicate a localised tumour if a large enough dose of radiation could be delivered to tumour, however, practically, there is always the danger of damaging normal tissues adjacent to the tumour. Factors such as the total radiation dose, overall treatment time, dose per fraction, dose-rate and the effects of changing the irradiated volume of the spinal cord have been examined in order to improve the therapeutic ratio in radiotherapy. The majority of these studies have concentrated on optimizing dose fractionation schedules. Only recently have attempts been made to modify this effect by the administration of therapeutic agents after irradiation but before the development of the lesion. Despite this interest the problem still exists. At present there is no effective clinically applied treatment towards radiation-induced normal tissue injury, however, some symptoms for example swelling or pain during inflammatory phase may respond to corticosteroids (Godwin-Austen 1975). There are a number of agents, which have been used experimentally, some clinically, to alleviate radiation damage. The results of these studies are reviewed here. A number of substances, generally named Biological Response Modifiers (BRMs), with diverse mode of actions have been used in post irradiation modification of normal tissue reactions. The effect and mode of action of a number of these treatments are discussed here. Classical radioprotectors, that are mainly thiol-containing substances such as Amifostine (Andreassen 2003), are used for prophylaxis and should be administered before or at the time of irradiation. These substances have been deliberately excluded in this article.

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### Steroids

#### *Experimental studies*

Steroids were possibly the first group of drugs exploited in the treatment of radiation lesions and its use has not always been beneficial. Early works used steroids mainly to alleviate acute inflammatory reactions. After an unsuccessful attempt by Smith (1950), Marshal (1953) demonstrated a beneficial effect of cortisone treatment (0.25 mg daily) starting 7 days after irradiation of mouse skin with single X ray doses of approximately 35 or 40 Gy. This treatment had no effect on the incidence of moist desquamation but significantly delayed the development of this lesion in animals treated with cortisone compared with animals treated with radiation only. Average delay in the development of lesion was about 7 days. Later, complete resolution of neurological deficit, resulted by delayed cerebral radiation necrosis, after corticosteroid therapy was reported (Martins 1977, Shaw and Bates 1984). This was

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followed by reports that steroids protected irradiated rat lung from early interstitial oedema, delayed the alveolitis without reducing its severity, significantly reduced the alveolar protein leak (Ward 1993[a]) and alleviated the reduction in total lung compliance in rats within one month of therapy (Moss 1960). However, it had no beneficial effect on the development of late fibrosis (Ward 1993[a]).

A topical application of prednisolone (0.5%) and NeAmycin (0.5%), twice daily, after radiotherapy reduced the area of moist desquamation of skin of cancer patients treated with a single dose of 22.5 Gy of X rays for basal cell carcinoma of facial skin (Halnan 1962). Methylprednisolone administered intraperitonealy alleviated interstitial oedema of the lung, delayed alveolitis and reduced leakiness of the lung after bilateral irradiation in rats (Ward *et al.* 1993[a]). Steroids also suppressed the severity of inflammation when administered throughout the period of alveolitis. Prednisolone administered just before and just after irradiation or after radiation pnueomonitis was developed reduced pulmonary lethality significantly in total body irradiated mice (Phillips 1975). However, death rapidly occurred when the drug was stopped.

While low doses of prednisolone (18 mg/kg, ip) showed some beneficial effect in reducing the combined action of cranial irradiation (10 Gy, single dose) and methotrexate in rats larger doses of prednisolone (36 mg/kg, ip) enhanced behavioural changes induced by a combination of radiation and methotrexate in young rats (Mullenix 1994).

Beneficial effects of steroidal anti-inflammatory drugs in reducing radiation-induced skin reactions were also reported in experimental models (Lefaix 1992) and it was shown that intramuscular injection of betamethasone 24 hours and 4 weeks after irradiation reduced moist desquamation of rabbit skin but had no beneficial effect on the development of late radiation-dermal necrosis. Results were the same when betamethasone was combined with Dexchlorpheniramine. Betamethasone combined with haemorheological agent Trimetazidine was effective until 4 weeks after irradiation. Dexamethasone (0.25 mg/kg daily) was reported to reduce vascular damage after X-irradiation of rabbit brain (Blomstrand 1975), which was monitored by vascular permeability.

Lurie and Casarett (1975) reported that adrenalectomy had a profound effect on the severity and progression of radiation-induced nephrosclerosis in rats. From comparison of their findings with those of Wachholz and Casarett (1970) these authors concluded that adrenalectomy only accelerated the development of nephrosclerosis after renal irradiation. It was suggested that glucocorticoids and /or corticosterone protect microvascular endothelium against excessive constrictive and permeability changes. Lack of adrenocorticoid in adrenalectomised rats have resulted in severe exacerbation of the permeability changes resulting from irradiation, therefore, accelerating the development of radiation induced nephroseclerosis.

Although, Brown (1956) observed remarkable modification in the response of rat lung to approximately 3Gy of X-rays with cortisone treatment overall he concluded that cortisone alone or in combination with Terramycin neither increased nor decreased survival of animals after thoracic irradiation. Steroid administration, even in small doses, adversely affected the survival of rabbits (Cladwell 1971) and rats (Berdjis 1960) after renal irradiation. Similarly, Stryker *et al.* (1976) reported that prednisolone had no beneficial effect on radiation-induced acute inflammatory reaction of the rectum in dogs and even increased the severity of the late tissue damage. Treatment with dexamethasone (2.9 mg/kg/day im) did not improve the survival of rhesus monkeys after brain irradiation (Martins 1979). No significant improvement with regard to the latency to onset or the incidence of neurological symptoms or severity of white matter necrosis was found. The only difference was about 14 days delay in the development of epilation of scalp by dexamethasone. Jacob *et al.* (1984) also reported the failure of dexamethasone on

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improving the survival of whole-body irradiated mice. Fleming (1962) also failed to modify the effects of irradiation on dog lung by cortisone.

***Clinical studies***

Abdelaal (1989) treated five patients receiving radiotherapy for malignant parotid tumours with 2mg betamethasone sodium phosphate dissolved in 15 ml water. The solution was used as a mouthwash for 2 mins, four times a day starting the day before and throughout 6 weeks radiation treatment period. This treatment prevented mucositis, erythema of mucosa and radiation-induced discomfort in all five patients. On the contrary, neither betamethasone (Baum 1989, Triantafillidis 1990) nor 5-Aminosalicylic acids, the active moiety of sulphasalazine, offered significant benefit in the treatment of radiation proctitis (Triantafillidis 1990).

***Conclusion***

Evidence on the use of steroids in the treatment of radiation injury is contradictory. Some authors have even reported adverse reactions of using corticosteroids for the treatment of radiation damage (Berdjis 1960, Cladwell 1971). Majority of the older publications, reporting the results of steroid therapy, suffer from poor study design and lack of randomised procedures. However, evidence based on the recent reports and randomised studies do not favour the beneficial effects of steroid therapy. It appears that, at its best, steroids may delay the development of acute lesions and perhaps reduce the severity of the lesions (Marshal 1953) with no effect on reducing the incidence of radiation lesions particularly late effects (Moss 1960).

A large number of reports are available on the administration of steroids prior to or during radiotherapy. This will reveal the drug's radioprotective properties rather than its modifying capabilities. Since the aim of this article was to review the BRMs, therefore, these reports are not included here. For a review of this material see Michalowski (1992).

**Non steroidal anti-inflammatory drugs**

Non steroidal anti-inflammatory drugs (NSAIDs) refer to a chemically heterogenous group of drugs that have a common property of inhibiting cyclo-oxygenase activity (Higgs and Vane 1989). It is generally accepted that NSAIDs act by inhibiting the synthesis of stable prostaglandins from arachidonic acid (Vane 1971). However, the action of NSAIDs appears to be more complex as these substances show other activities such as neutrophil activation or uncoupling oxidative phosphorylation that do not depend on inhibition of prostaglandin synthesis (Kitsis 1991). It is suggested (Abramson and Weissmann 1989) that while inhibition of prostaglandin synthesis might be the mode of action of some NSAIDs some others may act by inserting into the lipid bilayer of plasma membrane, and interfering with signalling and protein-protein interactions.

***Experimental studies***

Indomethacin is a potent prostaglandin synthesis inhibitor. Treatment with Indomethacin and Diclofenac sodium increased granulocyte counts in the blood of sublethally gamma-irradiated mice (Pospisil 1986, 1989); however, administration of sodium salicylate and Indmetacin together decreased the beneficial effects of Indomethacin. Rose (1992) reported less polymorphonuclear leukocyte infiltration and decreased tissue degeneration in Indomethacin treated rats after 50 Gy (single dose) of whole abdomen irradiation.

Indomethacin has been shown to be beneficial in reducing the severity of radiation induced oesophagitis in mice (Tochner 1990) and the opossum (Northway 1980).

*In vitro*, Indomethacin stimulated the proliferation of murine hematopoietic stem cells (Estrov and Resnitzky 1983) and administration of Indomethacin after sublethal (4 Gy TBI) irradiation of mice induced a rapid recovery of all nucleated spleen cell populations (Serushago 1987). This might be due to the enhancement of cell mobilisation from bone marrow rather than proliferation of splenic cells. However, when $PGE_2$ was administered together with

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Indomethacin the recovery of splenic cells diminished to the level of controls. This suggests that the restoration of splenic cells by Indomethacin was probably due to a diminished level of prostaglandins in the plasma of irradiated mice.

On the contrary, Hofer (1992) reported adverse reactions associated with the administration of Indometacin or Diclofenac after a total body dose of 10 Gy in mice. Administration of Indometacin (0.7-3.3 mg/kg, s.c.) or Diclofenac (5mg/kg, s.c.) two or 24 hours after irradiation significantly reduced the survival of mice after total body irradiation. All animals treated with Indometacin or Diclofenac died within 9 days after irradiation while over 50% of the animals in radiation only group were alive. Severe enteropathy, manifested by the swelling of lamina propria, irregularities of the mucosal surface and bending and cystic dilation of the crypts, was reported in these animals. Death was attributed to the enhanced leakage of endotoxin from the intestine. It appears that prostaglandin synthesis inhibitors that demonstrate a beneficial effect after sublethal doses or local irradiations of skin can have adverse reactions after lethal doses and irradiation of some other organs. Care must be taken in the administration of these substances for the management of different aspects of radiation damage (Hofer 1992). Administration of Indomethacin with sodium salicylate together even decreased the beneficial effects of Indomethacin in increasing granulocyte counts in the blood of mice after TBI (Pospisil 1989). Northway *et al.* (1988) tested a number of NSAIDs including Aspirin, Piroxicam with several doses and routes of administration, all starting before start of radiotherapy and continued for about 1 week after that, but did not observe any beneficial effect in development of radiation proctitis induced by 22.5 Gy single dose of X-rays in rat.

It is known that TNF-$\alpha$ stimulates the release of prostaglandins and IL-1 and prostaglandin $E_2$ is inhibitory to TNF secretion (Bachwich 1986, Kunkel 1988). Indomethacin enhances radiation induced TNF production (Petrini 1991), therefore, prostaglandins produced by cyclo-oxygenase pathway act as negative regulators of TNF. Suppression of this pathway may have exacerbated the effect of radiation seen by Hofer (1992).

Sodium meclofenamate, an anthranilic acid derivative similar to mefenamic acid, is usually given by mouth in muscloskelethal and joint disorders such as osteoarthritis and rheumatoid arthritis. This drug not only inhibits prostaglandin synthesis interferes with their interaction with cellular receptors. Ambrus (1984) treated radiation-induced esophagitis and cystitis in stumptailed monkeys (Macaca arctoides). Varying doses of sodium meclofenamate (5-20 mg/kg, daily by oral gavage) significantly reduced radiation-induced esophagitis during the three weeks of study. However, only the largest dose (20mg/kg) had a significant effect in reducing the radiation-induced cystitis. Radiation dose was 20 Gy delivered as a single dose to esophagus or pelvic area.

Administration of Flurbiprofene (3.3 mg/kg/day) alone or combined with Trimetazidine (1 mg/kg/day) for 8 weeks starting 24 hours after irradiation reduced moist desquamation of rabbit skin significantly (Lefaix *et al.* 1992). No beneficial effect was observed with Trimetazidine alone.

Enprostil, a synthetic $E_2$ prostaglandin, prevented the radiation-induced reduction in the intestinal mucosal surface area and body weight when orally administered (5 $\mu$g/kg) to rats for two weeks following abdominal irradiation (Keelan *et al.* 1992). However, the same treatment failed to improve the malabsorption of glucose in the same animals. Northway *et al.* (1988) tested prostaglandin $E_1$ analogue, Misoprostol, with several doses and routes of administration, all starting before start of radiotherapy and continued for about one week after that, but did not observe any beneficial effect in development of radiation proctitis in rats.

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***Clinical studies***

Nicolopoulos *et al.* (1985) reported milder endoscopic oesophagitis and symptomology in lung cancer patients who received Indomethacin after thoracic irradiation. However, histologic findings of oesophagitis was not different between Indomethacin treated and control groups. Villus/crypt ratio was not affected by Indomethacin.

Mennie and Dalley (1973) treated 15 women suffering from radiation-induced diarrhoea with 900 mg soluble aspirin four times daily. Diarrhoea was either abolished or improved in twelve of these patients that had failed to respond to conventional treatment. The work was followed up by the results of a randomised trial (Mennie *et al.* 1975) that reported that acetylsalicylate effectively controlled the diarrhoea and associated colicky pain and flatulence in 28 women who were receiving pelvic radiotherapy for uterine cancer. Ludgate (1985) treated eight patients with complications following pelvic irradiation with enteric-coated acetylsalicylic acid; Entrophen. While radiation enteritis was improved in all the patients who remained on Entrophen healing of epithelial ulceration was observed in four out of six cases and improved in one. Patients had to remain on Entrophen. One patient, who stopped Entrophen treatment after six weeks, experienced recurrent diarrhoea and cramps that resolved after restarting the treatment. The mode of action was suggested to be by interference with excessive production of prostaglandin after intestinal irradiation (Mennie *et al.* 1975). In contrary, Tanner *et al.* (1981) treated radiotherapy and chemotherapy induced mucositis in head and neck cancer patients with aspirin and observed no beneficial effect.

Benzydamine hydrochloride solution (1.5mg/ml) was given to 37 patients as mouth wash and gargle and compared with 30 patients who received only placebo mouth wash showed significantly reduced pain and delayed acute oral and oropharyngeal mucositis (Kim *et al.* 1986). The effect of Benzydamine hydrochloride was assessed on another group of patients (Epstein *et al.* 1989). This study reported a beneficial effect of Benzydamine hydrochloride only in terms of the size and severity of mucositis but it failed to prove beneficial in reducing the pain. Samaranayake *et al.* (1988) compared the effectiveness of Benzydamine hydrochloride solution and chlorohexidine as mouthwash on a small number of patients and found no difference in terms of mucositis, pain or the presence of micro-organisms. However, patient acceptance of chlorohexidine was found to be better. There was no placebo group; therefore, the study does not clarify whether any of the solutions had a beneficial effect.

***Conclusion***

There are conflicting results about the efficacy of NSAIDs in the treatment of radiation-induced normal tissue lesions. It should be borne in mind that the mode of action of all NSAID is not the same and they may have different action on radiation response of different tissues. The conflict could rise from using unsuitable drugs. While inhibition of prostanoid production, via cyclo-oygenase inhibition, after irradiation appears to be beneficial in some tissues it is undesirable in others. Overall, NSAIDs, notably Aspirin and perhaps Indomethacin appear to be effective in the treatment of acute radiation damage in some tissues. NSAIDs such as Indomethacin has been shown to be beneficial after sublethal TBI and local skin irradiations or aspirin in the treatment of mucosal reaction in radiation entretitis have adverse reactions after lethal doses and irradiation of some other organs such as rectum. This inconsistency in the response of irradiated tissues to NSAIDs is a cause for concern. Care must be taken in the administration of these substances for the management of different aspects of radiation damage. Twomey *et al.* (1992) tested twelve different NSAID and categorised them into three groups. Those that increased superoxide production (Diclofenac, Meclofenamate, Mefenamic acid), those that had no effect (Aspirin, Ketoprofen) and those that decreased superoxide production (Phenylbutazone, Piroxicam). It was concluded that the mode of action of those NSAIDs that

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caused enhancement of superoxide response was unlikely to be due to an inhibition of cyclo-oxygenase pathway. Perhaps this group of NSAIDs will not be suitable for the treatment of radiation lesions and this might be an explanation for the adverse reaction of Diclofenac treatment after total body irradiation in mice (Hofer *et al.* 1992). On the other hand NSAIDs such as Indomethacin, salicylic acid and acetylsalicylic acid (Aspirin) might be more suitable for this purpose as they have been shown to inhibit the superoxide generation by human neutrophils (Umeki 1990).

**Enzyme inhibitors**

***Angiotensin converting enzyme (ACE) inhibitor***

***Experimental studies***

On the basis of the effects of ACE inhibitors in prevention and treatment of progressive renal failure the role of Captropril was investigated in the treatment of radiation nephropathy in rats (Robbins and Hopewell 1986) and it was demonstrated that early haemodynamic changes after renal irradiation could be ameliorated. This was followed by a number of studies in lung by Ward *et al.* (1988, 1989, 1992[b]) who reported that ACE inhibitors could reduce the development of radiation-induced endothelial dysfunction and lung fibrosis. This work was extended to the study of radiation induced nephropathy (Cohen *et al.* 1992) and it was concluded that early intervention with ACE inhibitors preserved kidney function, reduced proteinuria and increased the survival of irradiated animals. Moulder *et al.* (1993) reported that both Captopril and Enalapril had comaparable effect in limmiting the development of radiation nephropathy in rats. Moulder *et al.* (1996, 1998[a]) also demonstrated that blocking angiotension II (AII) receptor was more effective than blocking the synthesis of AII with ACE inhibitors in the prophylaxis of nephropathy. Further studies by Captropril have shown that it inhibits histamine- and serotonin-induced vascular permeability in rat skin (Fantone *et al.* 1982) and ameliorates radiation damage to heart (Yarom 1993).

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***Clinical studies***

Wang *et al.* (2000) reported a retrospective study of incidental use of ACE inhibitors in 26 out of 213 lung cancer patients who receieved ACE inhibitors for hypertension during radiotherapy for lung cancer. These authors concluded that, within the dose range prescribed for hypertention, ACE inhibitors had no beneficial effect on the incidence or delay the onset of symptomatic radiation pneumonitis among lung cancer patients receiving radiotherapy. A placebo-controlled trial of captopril to prevent bone marrow transplantation nephropathy in adults is now underway (Moulder *et al.* 2003).

***Conclusion***

Despite clear understanding of the physiology of Renin-angiotensin system the mechanisms of action of ACE inhibitors on radiation-induced nephropathy is not fully understood. While there is ample evidence to support the efficacy of ACE inhibitors (captopril and enalapril) and AII receptor antagonist losartan in amelioration of radiation-induced nephropathy their clinical efficacy need to be proven.

**Antioxidants**

The process of oxidative stress is closely related to a complex cascade of events involving imbalanced production of certain cytokines. A recent hypothesis in the development of normal tissue lesions is the existence of a sustained oxidative stress or dysregulation of cytokines in irradiated tissues (Tofilon and Fike 2000). Because our antioxidant defences are not completely efficient, and even at its best it can only cope with a moderate increase in free-radical formation in the body, it is very likely that exogenous anti-oxidants might be beneficial in case of radiation exposure. Therefore, modulation of oxidative stress caused by

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irradiation may have a role in amelioration of radiation damage.

***Experimental studies***

In a standardised experimental pig model (Lefaix *et al.* 1996) radiation-induced lesions were produced on the skin, subcutaneous tissue and skeletal muscle of pigs with 160 Gy of photon irradiation. This is a substantially large dose that may mimic overexposure of humans in radiation accidents involving non-uniform irradiation of skin and subcutaneous tissue. Six months after irradiation, when a fibrotic scar was formed, intramuscular injection of (1mg/kg) of liposomal copper/zinc superoxide dismutase (Cu/Zn-SOD) or manganese superoxide dismutase (Mn-SOD), twice a week for 3 weeks, reduced the volume of the scar by 70%. The effect of the treatment was obvious from the first week of treatment. SOD has also been shown to reduce the severity of radiation-induced pulmonary lesions in rats (Malaker & Das 1988). It appears that a difference of six hours in the biological half-time of liposomal Cu/Zn-SOD (24 hrs) and free Mn-SOD (18 hrs) in pigs had no significant effect on the efficacy of SOD treatment as Lefaix *et al.* (1996) obtained similar results from Cu/Zn-SOD or Mn-SOD. However, it was reported (Gorecki *et al.* 1991, Parizada *et al.* 1991) that Mn-SOD was more effective than Cu/Zn-SOD in models of acute inflammation and chronic diseases.

***Clinical studies***

Baillet *et al.* (1986) treated 50 patients with established radiation fibrosis with twice weekly intramuscular injection of 5 mg liposomal superoxide dismutase for three weeks and observed a significant softening of the fibrotic tissue in 82% of the cases. This was followed by further reports from the same group that demonstrated the effects of systemic administration of SOD in the treatment of radiation fibrosis in a heterogeneous population of radiotherapy patients (Delanian *et al.* 1994).

***Conclusion***

These results of SOD reported by French scientists, particularly those of Lefaix *et al.* (1996) were the most significant modification of radiation damage to report that a radiation-induced fibrotic scar could be pharmacologically reversed after six months of irradiation. This was supported by clinical studies. The precise mechanisms by which liposomal or free SOD interact with fibrotic tissue are unknown. While scavenging effect of SOD can explain the radioprotective effect (when it is made available at the time of irradiation) of this substance its actual mechanism of action on reversing chronic conditions such as late skin fibrosis is not clear. Lefaix *et al.* (1996) postulated three possible mechanisms for the effects of SOD. Exogenous SOD might enhance weakened anti-oxidant capability of irradiated tissue, the attachment of SOD to cellular membrane initiates an anti-inflammatory process or inhibition of leukocyte and macrophage migration into the extravascular parenchymal tissue that might initiate fibroblast recruitment and proliferation. These explanations, however, remain to be proven. Overall, reported results of SOD treatment are remarkable. Most striking is the stability of the results after the patients have stopped treatment (Delanian *et al.*1994).

***Vitamin E***

α-Tocopherol that occurs in membranes and lipoproteins blocks the chain reaction of lipid peroxidation by scavenging intermediate peroxyl radicals and converting it to a tocopherol radical. This radical is much less affinitive in reacting with adjacent fatty-acid side-chains and can be converted back to α-tocopherol by vitamin C. Tocopherol has been mostly used in combination with other compounds in the treatment of radiation lesions.

Tocopherol, Troxerutine and Vincamine administered 24 hours after irradiation of the skin of rabbits, for 8 weeks, showed no beneficial effect (Lefaix *et al.* 1992), however, α-tocopherol in combination with Pentoxyfilline was significantly effective in softening and

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shrinking of fibrotic scar, developed 26 weeks after 160 Gy single dose gamma rays in pig skin (Delanian 1998, Lefaix *et al.* 1999).

### *Vitamin C*

Ascorbic acid, originally called vitamin C, is a ketolactone and a powerful reducing agent that accelerates hydroxylation reactions in a number of pathways. Ascorbic acid is a cofactor for prolyl and lysyl hydroxylates in the biosynthesis of collagen and is required for optimal function of many enzymes including proline hydroxylase, lysine hydroxylase (Mussini *et al.* 1967, Puistola *et al.* 1980). However, if ascorbic acid is replaced by other reductants these enzymes will still exhibit partial but not maximal activity (Levine 1986). Ascorbic acid has been considered helpful in treating patients with several types of cancer (Cameron and Pauling 1976) and enhances the synthesis of carnitine from lysine. Carnitine is essential for the transport of long chain fatty acids from the cytosol to the site of beta-oxidation in mitochondria (Levine 1986). Absence of ascorbic acid in the diet causes scurvy (Hodges 1980), capillary fragility due to a defect in the proline hydroxylation step in collagen biosynthesis (Mussini *et al.* 1967), fatigue, hperkeratosis of hair follicles, anaemia (Hodges *et al.* 1971). Ascorbic acid has been associated with certain aspects of the immune system, cholesterol metabolism but these are controversial (Levine 1986).

Narra *et al.* (1993) reported protection (DMF= 2.4 ± 0.4) of the spermatogonial cells in mouse testes against chronic irradiation by Vit C enriched diet (1% by weight). Similar results were obtained (Narra *et al.* 1993, Narra *et al.* 1994) by directly injecting into the testes of a very small dose of Vit C (1.5 μg in 3 μl). On the contrary, Abramsson-Zetterberg (1996) added 5% ascorbic acid to drinking water of mice a week before to five weeks after irradiation with low dose-rate gamma rays and did not observe any modification in the response assessed by measuring the frequency of micronucleated normochromatic erythrocytes (MNCE) in peripheral blood. These authors concluded that increasing the intake of ascorbic acid would not be effective in protecting against low doses of ionising radiation to which humans are normally exposed. The dose-rate studied by these authors was 44 mGy/day which is by far greater than the dose to which normal population are usually exposed. Furthermore, there is no evidence to correlate the level of MNCE and the development of long-term effects of radiation.

Although some studies show positive evidence on the efficacy of ascorbic acid in modification of radiation damage overall the evidence is not conclusive; because these studies have used mouse as an experimental model that might not be a suitable model to study the effects of ascorbic acid. Although humans are unable to synthesise ascorbic acid most other mammals including mice can do so from glucuronic acid or galactonic acid derived from glucose (Chatterjee 1970). Mouse can synthesise 33.6-226.0 mg/kg body weight/day of ascorbic acid. This makes the mice one of the most efficient mammals in producing its own ascorbate. Other animals unable to synthesise ascorbic acid include non-human primates, guinea pig, Indian fruit bats and several varieties of bulbuls. The inability of human in synthesising ascorbic acid is possibly due to lack of enzyme glunolactone oxidase or a counterpart (Levine 1986).

## Haemorrheological agents

### *Anticoagulants*

Application of anticoagulant, Heparin, as a BRM was one of the earliest attempts in the treatment of radiation-induced normal tissue lesions. Boys & Harris (1943) considered radiation pneumonitis as an inflammatory process and assumed that prevention of fibrin formation and elimination of thromboses and fibrosis of microvasculature would prevent radiation pneumonitis and subsequent fibrosis. Although these authors claimed an improvement of radiation damage to lung by the application of heparin, Fleming *et al.* (1962) failed to modify the development of radiation pneumonitis in dog lung by the same approach. A negative result was also reported by Moss *et al.* (1960) on the failure of Heparin as a BRM after thoracic

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irradiation. Another anticoagulant, Dicumarol, was unsuccessfully tried in modifying the development of radiation pneumonitis in human lung (Macht and Perlberg 1950).

***Pentoxifylline***

***Experimental studies***

Modifying effects of pentoxyfylline on the effects of radiation on cutaneous tissue has been studied in a mouse foot model (Dion *et al.* 1989). It was reported that pentoxifylline had no effect on acute radiation injury to mouse foot. The severity, the time course of development and recovery for the acute reactions were identical for the pentoxifylline and control animals. However, a significant effect on the development of late radiation damage was observed in pentoxifylline group. There were 4/41 (8%) radiation-induced late injuries in animals treated with a daily injection of pentoxifylline and 20/48 (42%) in control animals that received a daily saline injection as placebo. In these experiments Pentoxyfylline was administered during the course of irradiation. Lefaix *et al.* (1999) reported significant softening and shrinking of radiation-induced fibrotic scar, developed 26 weeks after 160 Gy single dose gamma rays, in the pigs treated with PTX (13.3 mg/kg/day) and α-tocopherol (17 IU/kg/day) for 13 weeks. Ward *et al.* (1992[a]) reported failure of pentoxifylline in modifying radiation pneumonitis in rat. The response was monitored by modification of radiation induced suppression of ACE and PLA activity and radiation induced elevation of prostacyclin and thromboxane production. The amount of hydroxyproline in the lung was measured as an indication of pulmonary fibrosis. The severity of epilation and desquamation of skin in the field of irradiation was scored weekly as a measure of early skin damage and it was concluded that pentoxifylline did not modify the acute skin lesions either.

***Clinical studies***

There is increasing evidence on the clinical efficacy of PTX. Dion *et al.* (1990) treated 15 sites of grade 4 radiation necrosis; four oral cavity, four mucosa of female genitalia, seven skin ranging from 2x3 mm to 3.5x18 cm with PTX (400 mg tid for 3 months, one patient qid) and observed that 87% (13/15) of necrosis healed completely, one partially, one failed to heal. Futran *et al.* (1997) treated 26 patients with radiation-induced normal tissue lesions after radiotherapy for head and neck malignancies with PTX (400mg, tid at least for 3months) and concluded that PTX accelerated the healing of soft tissue necrosis and reversed late radiation injury. PTX treatment was effective for significant number of patients; 9/15 (60%) with soft tissue necrosis healed completely, 3/15 (20%) partially and had no effect on 20%. Mucosal pain resolved in 5/5 (100%) and fibrosis resolved in 4/6 (67%) of those with fibrosis. The latency for the appearance of the lesions was >2 months after radiotherapy and the duration of the lesions ranged from 8 to 41 weeks prior to PTX treatment. PTX has been reported to relieve the pain due to radiation fibrosis (Werner-Wasik & Madoc-Jones 1993). This was in a 56-year-old female, treated for T1 adenocarcinoma with excision and re-excision of the lesion followed by radiotherapy, reconstructive surgery for severe tissue deficit at seven months post radiotherapy. Pain developed 3 months later. Treatment with PTX (400mg tds for 6 weeks) resulted in complete relief of pain and tenderness of fibrosis. Recently, significant relief of signs and symptoms of radiation mastitis in a small number of patients has been reported (Steeves & Robins 1998); oedema, erythema and pain started to resolve 3-4 weeks after start of treatment with PTX. Beneficial effect of a combination of Pentoxyfilline and vit. E in the treatment of radiation lesions has been reported by Gottlöber *et al.* (1996). This was followed by a report of regression of established radiation fibrosis, which had developed 10 years after irradiation, with with the same treatment (Delanian 1998).

Stelzer *et al.* (1994) reported an overall non-significant trend between the development of radiation lesions and coffee drinking habit of 82 cervical cancer patients treated with primary/adjuvant radiotherapy. Higher coffee

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consumption at the time of radiotherapy was associated with reduced late effects. The incidence of severe late effects was significantly (p=0.02) lower in heavy coffee drinkers. This was attributed to the protective effect of methylxanthines available in coffee.

***Conclusion***

Increasing experimental and clinical evidence suggests the efficacy of PTX in the treatmet of radiation injury; particlualry late effects. This introduces PTX, particularly combined with α-tocopherol, as an effective BRM. Our own studies (unpublished data) indicate that PTX (13.3 mg/day by oral gavage) reduces the incidence and the severity and accelerates the healing of radiation-induced moist desquamation of rat skin. However, results of Ward *et al.* (1992[a]) do not support this. Desquamation of rodent skin with dose of 0-30 Gy (Ward *et al.*1992[a]), can heel very rapidly perhaps within a few days. It would be possible to score only the severe reactions and severe reactions do not appear to be amenable for modification by BRMs. Therefore, scoring skin reactions in weekly intervals may have resulted in erroneous conclusions. This might be an explanation for the failure of PTX in reducing early skin reactions reported by Dion *et al.* (1989) too.

**Discussion**

Classical radiobiology, based on target theory for single cells, assumes that radiation kills cells at random and the dose of radiation and the radiosensitivity of irradiated cells determine the probability of cell kill. This concept was extended to tissues by viewing normal tissue radiation injury as a result of the sterilisation of clonogenic cells within that tissue. According to this concept tissue specific function is restricted to functional non-proliferative cells derived from clonogenic cells. Failure of clonogenic stem cells to replace the functional cells, which continue to be lost at a normal rate, results in a gradual depletion of functional cells. When the numbers of functional cells get to a critical level the tissue cannot sustain its function and radiation-induced injury is expressed. This concept views the latent period as a reflection of the turnover time of the target cells and considers the radiation damage inevitable and untreatable. Recent evidence, using new molecular techniques, indicates that a perpetual cascade of cytokines initiate immediately after irradiation that persist until expression of radiation injury. A number of processes such as gene expression, dysregulated cytokine production and oxidative stresshave already been identified. According to this view of the development of radiation injury latent period is not tenable and intervention at any stage of the complex process of the development of radiation lesion can potentially modify its progression. At present there is no panacea for radiation injury but evidence indicates to the possibility of modification of radiation-induced normal tissue damage by BRMs.

Dose and volume limitations imposed by normal tissue tolerance reduce the curability of localised tumours by radiotherapy except for radiosensitive tumours. Clearly, increasing normal tissue tolerance to ionising radiation or improved healing of radiation-induced lesions by BRMs can have significant clinical implications. This includes a variety of pharmacological approaches, by synthetic or naturally occurring substances. There is increasing evidence to suggest the involvement of prostaglandins in the development of radiation injury and substances that interfere with prostaglandin synthesis and eicosanoid metabolism appear to be the most widely studied mediators of radiation damage. This includes steroids, EFA and NSAIDs. However, there are several problems to enable us to translate the existing evidence to clinical practice. These include the conflicting results reported on some BRMs, the toxcitiy of these substances and the irradiation doses used in published reports. Conflicting results may rise partly due to differences in the pathophysiologic processes involved in the development of radiation lesions in different tissues and the markers used for the assessment of the efficacy of BRMs. These differences indicate to the complexity of the development of radiation damage and perhaps to the multiplicity of mechanisms involved.

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ACE inhibitors particularly Captopril and angiotension II (AII) receptor inhibitors in the treatment of radiation injury appear to be of value. However, major drawback of using Captopril is that the sparing effect is lost quickly on drug withdrawal.

Treatment results with SOD are remarkable. Striking effect of SOD is in the stability of the results after the patients have stopped treatment. However, evidence on the efficacy of ascorbic acid is not convincing but the data on the efficacy of α-tocopherol in combination with Pentoxyfilline and SOD in the treatment of late radiation damage are striking. Our own studies with antioxidants, although experimental, are very promising.

Pentoxyfilline alone has also shown significant beneficial effect in the treatment of late effects and recent evidence suggests that it might be beneficial for the treatment of acute lesions too. This needs further investigations.

Evidence on the use of steroids in the treatment of radiation-induced normal tissue lesions appears to be contradictory. Some authors have even reported adverse reactions of using corticosteroids and majorities of publications are old and suffer from poor study design and lack of randomised procedures. Evidence based on the recent reports and randomised studies do not always favour the beneficial effect of steroid therapy. It appears that, at its best, it may delay the development of acute lesions and perhaps reduce the severity of the lesions with no effect on reducing the incidence of radiation lesions particularly late effects.

There appears to be a tissue specific response for different NSAIDs. While some NSAIDs such as Indomethacin or aspirin prove to be beneficial after sublethal TBI and local skin irradiations or mucosal reactions in radiation enteritis they show adverse reactions after lethal doses and irradiation of some other organs such as rectum and oral mucosa. Although beneficial effects of using NSAIDs have been reported, however, a major draw back of using NSAIDs such as Aspirin in the treatment of radiation enteritis is that the patients have to remain on this medication. Care must be taken in the administration of these substances for the management of different aspects of radiation damage.

Overall BRMs appear to be more amenable for clinical use than other pharmacological substances such as classical radioprotectors (thiol compounds), hypoxic cell sensitisers or bioreductive drugs, where the toxicity has been either significant or unknown. However, not all BRMs might be non-toxic. While toxicity data are available for some BRMs, such as Pentoxifylline and ACE inhibitor Captopril are already in clinical use, detailed toxicity data are lacking for some BRMs. In some cases, like Penicillamine, toxicity has been studied in sufficient detail but only in rodent models. Detailed toxicity data will be required before the experimental data could be moved to clinical use.

Modifier effectiveness is usually expressed in terms of the dose modification factor (DMF), the ratio of the radiation dose in the presence of modifier and the radiation dose in the absence of modifier, required to produce the same level of injury. A DMF value of >1 is indicative of a beneficial effect, while values of 1 and <1 reflect no effect or detrimental effect, respectively. By definition DMF is the same as dose reduction factor (DRF) used in the literature. It is customary that DMFs are calculated from the comparison of $ED_{50}$, $LD_{50}$ values in quantitative analyses or from comparison of the response for known dose at a certain time point. In order to produce a meaningfully measurable level of damage, relatively larger radiation doses are employed in radiobiological research. These doses are often substantially larger than clinical doses employed in radiotherapy for cancer. The results of such studies might be applicable to the case of accidents but not directly to radiotherapy. The effects of BRMs should be demonstrated for doses comparable to clinical doses before the application of BRMs in clinical practice. However, lower incidence of the end points at the lower dose region of the dose-effect curve, where uncertainties are much greater, is a practical difficulty. This difficulty can be

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overcome by the study of modifying effects of BRMs at different dose points to demonstrate their efficacy at various dose levels. A true BRM should shift the dose-response curve towards higher doses by a constant fraction. Otherwise DMF will be a radiation-dose-dependent parameter. Furthermore, majority of the published experimental results on the efficacy of BRMs involve large single irradiation doses. Therefore, although encouraging, the compiled evidence have only limited value perhaps in the treatment of radiation accident patients or those with complications as a result of their radiotherapy for cancer. Studies involving full dose-effect curves are required to distinguish true BRMs, with a significant DMF that is constant for all dose levels. DMFs in excess of 1.13, and sometimes as high as 1.51, have been observed. This might appear modest but in reality dose increases of 10-20% above the present radiotherapy dose would, for many tumours, provide a significant local tumour control by radiotherapy. This is due to the steep dose response relationship for both normal tissue response and some tumours. Furthermore, fractionated radiotherapy is employed in curative treatments; therefore, BRMs need to be assessed in relation to fractionated schedules. Single dose data cannot be translated for clinical use, particularly for dose escalation purpose in radiotherapy, unless further results involving multiple small fractions, comparable to radiotherapy regimens used for the treatment of cancer patients, are made available.

Finally, evidence suggests that radiation insult, like many other tissue injuries, is amenable to drug treatment. Although, late effects such as skin or pulmonary fibrosis have always been considered as irreversible, the evidence suggests that even these lesions are amenable for modification. Radiation lesions ought to be considered as other pathological conditions and radiation medicine should utilise the findings of the other branches of medicine by exploiting common pathophysiologial developments between radiation lesions and other ailments. Systematic screening of synthetic and natural substances may lead to the identification of other BRMs that may modify the response of normal tissues more effectively.

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